Develop New or Improved Approaches for Preventing or Delaying the Onset or Progression of Disease and Disability

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Gene May Boost Estrogen-related Heart Protection

Background: Early in life, women have a relatively low incidence of atherosclerosis, marked by fatty accumulation along artery walls. But after menopause, with its accompanying loss of natural estrogen production, women are at high risk of developing atherosclerosis. This has led many to conclude that estrogen must somehow be protective of coronary arteries, and that hormone replacement therapy (HRT) might help reduce some cardiovascular problems in postmenopausal women. However, scientific studies examining this issue have reached varying conclusions. Some researchers suspect that genetic factors may underlie estrogen's apparently variable effects on cardiovascular health.

Advance: Researchers at Wake Forest University School of Medicine have identified a common genetic variant that appears to favorably affect postmenopausal response to estrogen. The scientists analyzed specific genes and cholesterol levels in 309 postmenopausal women who had heart disease and took either HRT or a placebo. About one in five of the women had specific variations in the gene that encodes the estrogen receptor-alpha (ER-_), which produces a cell-surface molecule that binds to estrogen. When women with these genetic variants began to take HRT, they had dramatic increases in blood levels of high-density lipoprotein, the so-called "good" cholesterol, which has previously been linked to prevention of heart disease. The boost to HDL levels in these women was more than double that of women on HRT who had other genetic variants of the ER-_ gene.

Implications: Genetic screening may eventually help identify postmenopausal women who respond favorably to HRT, allowing patients and physicians to better assess potential risks and benefits. Knowledge of the effects of genetic variants may also lead to new understanding of estrogen action and cholesterol regulation.

Herrington DM, Howard TD, Hawkins GA, et al: Estrogen-receptor polymorphisms and effects of estrogen replacement on high-density lipoprotein cholesterol in women with coronary disease. N Engl J Med 346(13): 967-974, 2002.

Disparities in the Diagnosis and Treatment of High Serum Cholesterol

Background: Elevated serum cholesterol (hypercholesterolemia) is one of the most important modifiable risk factors for coronary artery disease, and cholesterol-lowering drugs have been shown to significantly reduce the risk of developing coronary heart disease (CHD). The National Cholesterol Education Program recommends measuring serum cholesterol in all adults over 20 at least once every five years. Cholesterol screening rates have steadily increased during the past 20 years, and reduced death rates from CHD in recent years have been attributable to both screening and pharmacological treatment of hypercholesterolemia. However, the decline in death rates from CHD has been more significant in whites than in minority populations in the United States, although data suggest that the proportion of individuals with an elevated cholesterol level is similar across different racial and ethnic groups. This observation raises the possibility that disparities in the diagnosis and/or treatment of high serum cholesterol could account for these differences.

Advance: To assess the effects of race and ethnicity on cholesterol screening and treatment, researchers at Charles R. Drew University and elsewhere analyzed data from the more than 15,600 participants in the Third National Health and Nutrition Examination Survey, administered between 1988 and 1994. These data permit examination of time trends in treatment, since cholesterol-lowering drugs (statins) became available to the public in 1987. Analysis of the data revealed that African Americans and Mexican Americans were significantly less likely than whites to have had their blood cholesterol checked or to take prescribed cholesterol-lowering medications. Ethnic and racial differences in screening for high cholesterol persist even after accounting for the independent effects of income, education level, health insurance status, co-morbid disease, and having a regular source of health care. This suggests that lower rates of cholesterol screening in African Americans and Mexican Americans are due to other factors, in addition to problems with health care access.

Implications: The description of racial and ethnic variation in the primary prevention of CHD adds to the growing literature on disparities in health care in the United States. This work also points to the need for further research to understand the interactions between patients, physicians, and organizations that contribute to racial and ethnic variations addressing CHD.

Nelson KN, Norris K, Mangione C: Disparities in the diagnosis and pharmacologic treatment of high serum cholesterol by race and ethnicity. Arch Intern Med 162: 929-935, 2002.

Flu Vaccine is Safe for Adults and Children with Asthma

Background: Influenza causes substantial morbidity in children and adults with asthma, which disproportionately affects those who are poor and live in inner cities. Flu sends many asthmatic children to the hospital each year, and adult asthmatics with flu may suffer prolonged reduction in lung function. Although most people with influenza recover completely after 1 to 2 weeks, some people develop serious and potentially life-threatening medical complications. Annual flu vaccination is considered the most important step for preventing flu-related illness and death in those at increased risk for influenza complications, including people over the age of 65. Although individuals with asthma are also considered at risk for influenza complications, fewer than 10 percent of asthmatics currently receive flu shots, in part because of fear that the shot might induce an asthma attack. In contrast, almost 70 percent of people older than 65 in the general population obtain annual flu shots.

Advance: To study the safety of flu shots, researchers at the University of Vermont College of Medicine took part in a multi-center study of 2,032 people (ages 3 to 64) with asthma. Each participant was randomly chosen to receive either a flu shot or an identical-appearing placebo shot. For the next two weeks, participants kept a diary of their ease of breathing each morning, asthma medications they took, asthma-related trips to the doctor, and days missed from school or work due to asthma. Then the two groups switched and received the other shot. By the end of the month-long study, each participant had received a flu shot. Results showed no significant differences in asthma symptoms reported by the two groups within two weeks after a shot, whether it contained vaccine or placebo. The similarity in symptom rates was consistent in subgroups of participants defined by age, asthma severity, and other factors. Among vaccine-associated symptoms, only body aches were 4 percent more frequent following influenza vaccine compared to placebo.

Implications: The inactivated influenza vaccine is safe to administer to children and adults with asthma, regardless of asthma severity. Given the substantial morbidity of influenza, all individuals with asthma should receive the inactivated influenza vaccine annually.

Castro M, Dozor A, Fish J, Irvin C, et al: The safety of inactivated influenza vaccine in adults and children with asthma. N Engl J Med 345(21): 1529-1536, 2001.

Genetically Identical Monkeys Useful for AIDS Vaccine Studies

Background: The demand for rhesus macaques in biomedical research has increased significantly in recent years. If all monkeys used in an experiment were genetically identical, fewer monkeys would be needed to produce statistically valid results.

Advance: Researchers at the Oregon National Primate Research Center have evaluated two approaches for producing genetically identical monkeys. In one approach, the researchers separated the cells, called blastomeres, in two- to six-day-old embryos. All blastomeres in an early embryo have the same potential to become an embryo. The other approach involved splitting, or bisecting, seven- to eight-day-old embryos into two equal halves, both of which have the same potential to develop into embryos. The blastomeres and bisected embryos were inserted into the oviducts of recipient females. Although both approaches yielded a 33 percent pregnancy rate, the initial pregnancies did not result in live births. However, subsequent to publication of the study cited below, 10 additional pregnancies were achieved and two live births occurred. The animals born were positive for a Major Histocompatibility Complex (MHC) class I molecule called Mamu A*01. MHC class I molecules present viral fragments to certain immune cells to stimulate a coordinated immune response against that virus. Mamu A*01, which is found in rhesus macaques, helps to stimulate an immune response against simian immunodeficiency virus (SIV). This virus is closely related to human immunodeficiency virus and infects monkeys, producing a disease similar to AIDS.

Implications: Scientists interested in developing an AIDS vaccine have been requesting rhesus macaques with defined MHC types. Such animals will enable them to test possible SIV vaccines, and the information gained will help in the development of an AIDS vaccine. These animals will also be important for other studies requiring animals of known immunological competence.

Mitalipov SM, Yeoman RR, Kuo HC, Wolf DP: Monozygotic twinning in rhesus monkeys by manipulation of in vitro-derived embryos. Biology of Reproduction 66: 1449-1455, 2002.

Trial Demonstrates That Type 2 Diabetes Can Be Prevented or Delayed

Background: Type 2 diabetes affects almost eight percent of U.S. adults, and this percentage is expected to increase dramatically as the population ages and becomes more sedentary and overweight. If this trend continues, a frightening new wave of type 2 diabetes will threaten the health of many Americans and the health care system. Even with treatment and frequent monitoring to control their blood sugar, blood sugar levels are usually substantially above normal and most patients eventually develop complications such as kidney failure, amputations, cardiovascular disease and stroke, eye disease, and nerve damage. A critical research objective is to find ways to prevent the onset of type 2 diabetes and thus to avoid the enormous personal and societal costs of diabetes and its devastating complications. Research has shown that those at increased risk of developing diabetes can be identified based on blood glucose measurements, as well as other risk factors.

Advance: Building on advances in behavioral and pharmacologic research, researchers tested the effectiveness of drug and lifestyle interventions in preventing type 2 diabetes in an at-risk population. Participating patients were considered at-risk due to being overweight and having elevated fasting and/or two hour post-glucose-challenge blood sugar. Forty-five percent of the study population was comprised of minority groups at increased risk for diabetes. Three groups were compared: those who received standard lifestyle recommendations plus metformin (a drug used to treat diabetes), those who received standard lifestyle recommendations plus a placebo (inactive) drug, and those who participated in an intensive program of lifestyle modification, including both diet and exercise interventions. The intensive lifestyle modification was able to reduce the incidence of diabetes by a remarkable 58 percent, and treatment with metformin reduced the incidence by 31 percent, as compared to the placebo group. The diet and exercise intervention was significantly more successful in preventing diabetes than metformin, especially among older participants. Similar results were seen in all the racial and ethnic groups who participated and in men and women.

Implications: This trial demonstrates, for the first time in an American study population, that it is possible to delay or prevent the onset of type 2 diabetes in those at high risk for the disease, and that diet and exercise are more effective than drug treatment with metformin. Health care providers now have a powerful new method to help those most at risk to prevent or delay disease onset. By using these new tools, physicians and other providers can help to stem the rising tide of type 2 diabetes that is threatening the public health in the U.S.

Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346(6): 393-403, 2002.

Strict Blood Sugar Control Helps Prevent Long-Term Complications of Type 1 Diabetes

Background: In 1993, scientists completed a large randomized and controlled clinical trial to definitively test the hypothesis that elevated blood sugar causes complications in diabetes. This trial was called the Diabetes Control and Complications Trial (DCCT). Type 1 diabetes patients in the DCCT trial were treated with either intensive or conventional blood sugar therapy. Patients were tested on a regular basis to identify onset or progression of complications. Intensive blood sugar therapy dramatically reduced the incidence of eye, nerve, and kidney disease, as compared to those treated with conventional therapy. The risk of developing these complications was directly related to the patient's average blood sugar during the period of the trial. The positive effects of intensive treatment were so conclusive that the trial was halted prematurely at six and a half years, and patients in the conventional treatment group were encouraged to change to intensive treatment during a closeout phase.

Advance: In a follow-up study to the DCCT, scientists recently reported that the benefits of strict blood sugar control first observed in the DCCT persist for at least seven years after the trial ended. When the trial ended, both groups were encouraged to use intensive therapy and were closely monitored. Overall blood sugar levels soon became similar in the two groups – with better control in the former conventional group and looser control in the former intensive group. Despite their similar levels of control during the subsequent seven years, follow-up showed that those who had initially been in the intensive therapy group were still less likely to develop eye or kidney disease than those whose blood sugar was initially controlled using conventional therapy. This follow-up is part of the Epidemiology of Diabetes Interventions and Complications (EDIC) study, which is still ongoing. Using the DCCT closeout examination results as a baseline for comparison, the scientists found that for patients initially in the intensive treatment group, progression of retinopathy was reduced between 66 and 77 percent, and the risk for progression or development of decreased kidney function, as indicated by the presence of protein in the urine, was decreased by 84 percent. Prevalence of high blood pressure, an almost inevitable consequence of reduced kidney function, also differed between the former intensive and conventional DCCT treatment groups. Six years after the beginning of EDIC, 33 percent of those who had initially practiced conventional blood sugar control developed high blood pressure, as compared to only 25 percent of those who had practiced intensive control.

Implications: The DCCT results demonstrated that by strictly monitoring and controlling their blood sugar, patients can significantly reduce their risks of developing complications. The new results from EDIC show that the benefits of a finite period of stricter blood sugar control persist for at least seven years after levels of control were equalized. Because of this proven, persistent benefit, it is important to begin intensive treatment as early as possible. Although the study was done in patients with type 1 diabetes, it is likely that the results apply to all forms of diabetes. If doctors and patients adopt stricter standards of blood sugar monitoring and control, it is likely that we can prevent or delay the development of complications in the 17 million American with diabetes.

The Writing Team for the Diabetes Control and Complications Trial: Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. JAMA 287(19): 2563-2569, 2002.

Working to Eliminate Diabetes Health Disparities

Background: Many minority groups have an increased risk of developing type 2 diabetes. Moreover, minorities who develop type 2 diabetes tend to suffer more from complications of the disease than do Caucasians. To a large extent, the reasons for these health disparities are not fully understood.

Advance: Working with several minority communities, researchers have made progress towards establishing methods to manage, predict, describe, and reduce the risk of type 2 diabetes and its complications. In one study, researchers tested a culturally-appropriate diabetes self-management intervention in a Mexican-American population with diabetes. From a Texas county with one of the highest diabetes-related death rates, they selected a random sample of Mexican-Americans between 35 and 70 years of age who had developed type 2 diabetes after reaching age 35. In the experimental group, bilingual Mexican-American nurses, dieticians and community workers provided instruction in diabetes self-management, nutrition, and exercise, as well as six months of biweekly support group sessions to promote behavioral changes. A control group received no instruction aside from their normal medical check-ups. Patients in the experimental group had lower average blood sugar at six and 12 months and higher diabetes knowledge scores than patients in the control group. Thus, researchers demonstrated that a culturally-appropriate diabetes self-management intervention in Mexican Americans can significantly improve their blood sugar control and diabetes knowledge, and thereby potentially reduce their likelihood of developing complications.

A second study reported the prevalence rates of acanthosis nigricans (AN) and elevated insulin levels in Cherokee Indians aged 5-40 years. AN is characterized by dark, coarse, thickened skin most commonly found on the back of the neck. AN is common among African Americans, Hispanics, and American Indians but is rarely observed in Caucasians. It is associated with hyperinsulinemia, or high levels of insulin – a known precursor of type 2 diabetes. Researchers performed blood tests, medical exams, personal interviews, medical histories, and neck examinations for AN on members of the Cherokee Nation. They found that 34 percent of participants had AN and 47 percent had hyperinsulinemia. The rates of AN and hyperinsulinemia were higher in those who were older, female, more overweight or obese, had a higher degree of Indian heritage, those who already had type 2 diabetes, and those whose parents had or have type 2 diabetes. Presence of AN was found to be associated with hyperinsulinemia and may serve as a useful early indicator of high risk for diabetes in populations with high prevalence of AN. The AN skin exam is a simple, inexpensive and noninvasive way to predict risk of type 2 diabetes prior to disease onset and before complications arise. Early risk prediction provides an opportunity to intervene and possibly prevent onset of type 2 diabetes.

In a third disparity-related study, researchers compared the prevalence of type 2 diabetes in Filipina women (Filipinas) to the prevalence of the disease in an age-matched Caucasian population living in the same county. They found that Filipinas have a sixfold higher risk for type 2 diabetes even when they were not classified as obese according to western standards such as the Body Mass Index (BMI). Compared to their Caucasian counterparts, Filipinas also had a

threefold greater risk of developing the metabolic syndrome, a combination of at least three of the following: obesity, insulin resistance, diabetes or pre-diabetes, high blood pressure, and high blood cholesterol. Since BMI seemed to be a poor predictor of diabetes risk in Filipinas, the investigators searched for another possible predictor. They found that waist circumference and high levels of "bad" cholesterol were independently associated with risk of diabetes in Filipinas. This study demonstrates that BMI does not necessarily predict type 2 diabetes risk in all populations, and more studies must be done in order to develop accurate ways of predicting prevalence and risk of the disease in specific racial and ethnic groups.

Implications: These studies show that researchers are advancing the frontiers of knowledge about diabetes in minority populations in a wide array of areas, ranging from identifying risk factors for diabetes in specific populations to developing culturally sensitive, effective interventions to reduce risk and improve diabetes management. As our understanding of the causes of minority health disparities increases, and as we develop new tools to address these disparities, so, too, will our ability to eliminate these racial and ethnic disparities associated with type 2 diabetes increase.

Araneta MRG, Wingard DL, Barrett-Connor E: Type 2 diabetes and metabolic syndrome in Filipina-American women: a high-risk nonobese population. Diabetes Care 25(3): 494-499, 2002.

Brown SA, Garcia AA, Kouzekanani K, Hanis CL: Culturally competent diabetes self-management education for Mexican Americans: the Starr County Border Health Initiative. Diabetes Care 25(2): 259-268, 2002.

Stoddart ML, Blevins KS, Lee ET, Wang W, Blackett PR: Association of acanthosis nigricans with hyperinsulinemia compared with other selected risk factors for type 2 diabetes in Cherokee Indians: the Cherokee Diabetes Study. Diabetes Care 25(6): 1009-1014, 2002.

Stigma, Delayed Treatment and Willingness to Inform Contacts about STDs

Background: Sexually transmitted diseases (STDs) represent a public health issue because they affect the most economically active segments of the population and, particularly if left untreated, can result in serious complications that include sterility and birth defects. While STD control was successful following the revolution in China during the 1950s, since the more recent open door policy which began1980s and the more recent changes in sexual norms, STDs have become a public health problem once again; the average annual incidence doubled in the 5 year period between 1993 and 1998. Stigmatization, delayed treatment seeking behavior and unwillingness to notify partners are important for STD prevention and control. Little is known about the health care seeking behavior of STD patients in China.

Advance: Research collaborators from the University of California, Los Angeles, together with those from Anhui and Nanking, China, conducted a survey among approximately 400 men with STD symptoms seeking care at four urban clinics in the capital city of Anhui province. Participants completed a questionnaire; those with urethral discharge or painful urination were tested for gonorrhea and chlamydia, and those with genital ulcers were tested for syphilis and herpes. Among the men with urethral discharge or painful urination, almost half had gonorrhea, nearly 10 percent had chlamydia and about 15 percent had both gonorrhea and chlamydia. Among the men with genital ulcers, about one quarter had syphilis and one quarter had herpes. Both delay in seeking treatment and unwillingness to inform a spouse, were associated a lower level of education. Men who felt stigmatized were less likely to agree to notify their spouse; among married participants, three out of four expressed an unwillingness to do so. Feelings of stigmatization were not however associated with delay in seeking treatment. Explanations for this result includes the possibility that discomfort as a result of the infection which is more common in males with STDs, may outweigh the fear of stigmatization.

Implications: Because the duration of infectivity is a key variable in STD transmission, ensuring prompt and effective treatment of infected individuals is an essential public health measure. Given that STDs have strong synergistic effect on HIV infection, this study underscores that delayed treatment seeking, perception of stigma and failure to notify sexual contacts are major interrelated factors, all of which have important implications for STD control programs. Intensive education and effective counseling to reduce or eliminate stigma and efforts to increase the notification of contacts should be made available to patients with STDS, sexually active people and the general population around the globe.

Liu H, Detels R, Li X, Ma E, Yin Y: Stigma, Delayed Treatment, and Spousal Notification among Male Patients with Sexually Transmitted Disease in China. Sexually Transmitted Diseases 29(6): 335-343, 2002.

Prevention of Mother to Child HIV Transmission: Preferences of Zambian Women

Background: Prevention of HIV transmission from infected mothers to their babies has been simplified with the introduction of an effective drug called Nevirapine given to the mother once during labor and once to her newborn. Prior to administering the regimen however, one key requirement is knowledge of the woman's HIV status. In Lusaka, about $5 per patient per year is allocated for obstetrical care and no funds are allocated to support VCT. One controversial cost effective strategy under these conditions is treatment of all women during labor and their newborns, especially when HIV rates of infection among pregnant women are high; one such setting is Lusaka, Zambia, where nearly one-third of the pregnant women are estimated to be HIV infected. However, before introducing a strategy of this nature, it is important to understand how acceptable this approach would be to the pregnant women themselves.

Advance: Researchers from the Zambian Ministry of Health and University of Alabama conducted a questionnaire among pregnant women attending an antenatal clinic. Among the participants, over one-third had already had a delivery during which a child had died. Less than 1 percent of the women surveyed had undergone HIV testing, although almost nearly one-third acknowledged their own risk of HIV infection as moderate or high. Approximately 75 percent of women preferred the option of "test me for HIV and give me the treatment only if I am infected." While few (3 percent) did not want the test or treatment at all, the remaining 25 percent of women preferred not to know their HIV status but wished to receive the treatment even so, suggesting that this group wanted to avoid the possible stigma of being labeled with AIDS. When faced with the second question in resource-poor scenario to test and treat everyone, 60 percent of women though that Nevirapine should be offered to all women without HIV testing. The remaining 40 percent indicated that offering HIV-testing and drugs to half of the women was acceptable. Women who acknowledged their risk of HIV infection to be moderate or high were more likely than those with no or low perceived risk to choose mass therapy as the preferred option in the first question. The women in the moderate to high-risk group were not more likely to choose this option under the scenario with inadequate resources.

Implications: With the recent commitment by the manufacturer to donate Nevirapine in low resource settings, there is continued pressure to consider mass administration of the drug. Data from an urban area of Zambia shows that universal treatment is acceptable to pregnant women if costs preclude universal HIV diagnosis prior to treatment. Women's preferences should be considered as program policies are developed in Africa and elsewhere.

Sinkala M, Stout JP, Vermund SH, Goldenberg RL, Stringer JS: Zambian women's attitudes toward mass nevirapine therapy to prevent perinatal transmission of HIV. Lancet 358: 1611-1612, 2001.

Moderate Alcohol Use Reduces Heart-Disease Risk in Men with Adult-Onset Diabetes

Background: Type 2 diabetes, which first appears during adulthood, is the most common type of this disease. One of the biggest risks that people with diabetes face is deposits of fatty plaques in arteries – atherosclerosis – which can occur in blood vessels throughout the body. About 80 percent of people with Type 2 diabetes die from consequences of atherosclerosis. When atherosclerosis occurs in the arteries that supply the heart itself with blood, coronary heart disease (CHD) results.

Evidence that moderate alcohol use reduces risk of heart disease in the general population is mounting. Four recent studies asked whether moderate drinking also reduces risk of CHD in Type 2 diabetics, an especially high-risk group, and found evidence to suggest that it does. However, researchers needed to clarify whether other health and lifestyle factors might have contributed to alcohol's apparent protective effect. In this study of men with Type 2 diabetes, scientists performed statistical analyses that isolated alcohol's effect from a number of other factors. They also asked whether the kind of alcohol consumed – beer, wine, or spirits – is a factor.

For 10 years, researchers gathered data about the health and lifestyles of 2,419 men with Type 2 diabetes. Among the questions researchers asked was how much and how often study participants drank in the past year. Researchers also examined body mass, smoking, family history of heart attack, high blood pressure, high cholesterol, duration of diabetes, physical activity, vitamin E supplements, and dietary intake of fats, fiber, and folate (part of the B-vitamin complex).

Advance: Moderate drinking was associated with lower risk of CHD in men with Type 2 diabetes, regardless of the kind of alcoholic beverage consumed. The association held true when other health and lifestyle factors were eliminated as potential contributors to this effect.

Implications: If scientists can discover the biological mechanisms that underlie alcohol's protective effect, they can attempt to develop medications that mimic or enhance them. Type 2 diabetics who must avoid alcohol for any one of a number of important reasons could then reap alcohol's apparent benefits without its inherent risks. At this time, clinicians can't make blanket recommendations about alcohol use for diabetic patients.

Examples of reasons that diabetics and others might be prohibited from even moderate alcohol use are psychiatric problems, a history of drinking problems (or family history of drinking problems), or potential for medication interactions with alcohol. Heavy drinking has serious health consequences and shouldn't be advised for anyone. In Type 2 diabetes, it increases risk of nerve and retinal damage, among other serious or fatal problems.

Tanasescu M, Hu FB, Willett WC, Stampfer MJ, Rimm EB: Alcohol consumption and risk of coronary heart disease among men with Type 2 diabetes mellitus. J Am Coll Cardiol 38(7): 1836-1842, 2001.

Drug Prevention Interventions Needed Early

Background: A number of studies have reported on the age of greatest risk for initiating drug or alcohol use, as well as the likelihood of developing dependence once drug use has occurred. However, research has not previously focused on how quickly the transition from first use to dependence proceeds, and whether it is the same for differing drugs of abuse. Knowledge about this factor could be used in both prevention and treatment efforts, in order to better target messages and optimize the timing of interventions.

Advance: Using data from the National Comorbidity Survey, which includes information from 8098 respondents from the 48 contiguous states, ages 15-54, researchers examined a number of variables related to the timing of drug initiation and dependence for alcohol, marijuana, and cocaine. The age at which most people begin to use alcohol and marijuana was 18, earlier than cocaine, which peaked at age 20. However, once use began, cocaine dependence emerged rapidly, with 5 percent of cocaine users becoming dependent within the first year, and 15 percent becoming dependent within 10 years. Most of those who became dependent on cocaine did so within three years after drug initiation. The course for marijuana and alcohol dependence was slower, and more insidious. The risk of becoming dependent within 10 years was 8 percent for marijuana and approximately 12 percent for alcohol. Thereafter, the risk for developing marijuana dependence dropped to almost zero, while the risk for alcohol dependence continued at a low rate into middle age.

Implications: The optimal timing for prevention and treatment for substance abuse differs for different drugs. Educational messages should convey the differential risks associated with the onset of cocaine, marijuana, and alcohol use, highlighting the potential for rapid development of dependence on cocaine. Interventions to prevent cocaine abuse should be initiated rapidly, once cocaine use has begun, and efforts to prevent alcohol dependence need to be continued over a long period of time, possibly throughout the lifetime. Further research is necessary to elucidate the patterns of drug- taking that lead to dependence, as well as the effects of dosage and method of drug administration.

Wagner FA, Anthony JC: From first drug use to drug dependence: Developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. Neuropsychopharmacology 26(4): 479-488, 2002.

Elementary School Programs that Emphasize Social Development Reduce Risky Sexual Behaviors Into Adulthood

Background: Pregnancy and sexually transmitted disease rates continue to increase among adolescents. Each year, 10 percent of American females aged 15-19 years will become pregnant, and roughly half of them will give birth. Adolescents and adults younger than 25 years are also more likely to acquire STDs than older adults. Determining effective ways to prevent risky sexual behavior among our Nation's youth is an important national need.

Advance: Youth development programs targeted at elementary school students may have the potential to help youth acquire healthy behaviors that can be sustained across their life spans, including reducing risky sexual practices. The Seattle Social Development Project (SSDP) was administered in eighteen public elementary schools serving high crime areas of Seattle WA. Rather than targeting specific risk behaviors, the SSDP intervention promotes bonding to the school and family by enhancing opportunities and reinforcing children's active involvement in family and school. There is no sex education component to this intervention. The program has a teacher training component, child support and emotional development curriculum, and a voluntary parent-training component. The children received the intervention for at least one semester in grade 1, 2, 3, or 4 and for at least one semester in grade 5 or 6. 93% of the fifth grade students enrolled were interviewed at age 21. Those who received the full intervention reported significantly fewer sexual partners and had their first sexual experience significantly later than those who did not receive the intervention. Those in the intervention also were less likely to become pregnant and to have a baby by age 21 years old.

Implications: Theory based interventions that focus on supporting the promotion of academic success, social competence and social bonding as early as elementary school can have long lasting benefits. Although there was no sexual education component to this elementary school intervention, nor any discussion of sex at all, the follow-up study shows that enhancing social development in the elementary school period can reduce risky sexual behavior through age 21 years.

Lonczack HS, Abbott RD, Hawkins D, Josterman R, Catalono: Effects of the Seattle Social Development Project on Sexual Behavior, Pregnancy, Birth, and Sexually Transmitted Disease Outcomes by Age 21 Years. Arch Pediati Adolesc Med 156: 438-447, 2002.

Depression, Peers, and Tobacco Advertising: Their Role in Adolescent Smoking Decisions

Background: Tobacco use remains the leading preventable cause of death in the United States. Determining why so many adolescents start and continue to smoke despite the associated risks remains an important public health question. A number of social and psychological factors, such as positive attitudes and beliefs about smoking, the number of friends who smoke, and psychopathology, all have been identified as increasing the odds that an adolescent will become a smoker. Researchers were interested in determining the relationship of at least three variables to smoking: exposure to others who smoke, tobacco advertising, and depression.

Advance: 1124 ninth grade students in VA public schools participated in the study. The freshmen completed a 30-minute confidential self-report survey onsite during health and physical education courses. Information about smoking practices, demographics, exposure to environmental smoking, depression, and the influence of tobacco advertising on cigarette use were the main areas being addressed. The results were that approximately 60 percent of the participants identified themselves as non-smokers. Those who did smoke reported greater exposure to peers who smoked. Also those most vulnerable to smoking showed a significant relationship between high receptivity to tobacco advertising and clinically significant depressive symptoms. Overall, the adolescents with the highest level of depressive symptoms had a stronger tendency to fall into the smoking group. The R.J. Reynolds "Camel" products remain strong among youths.

Implications: Improving our understanding of the social and psychological interactions involved in smoking will improve our ability to identify those most at risk to becoming smokers and to develop tailored anti-tobacco health promotion messages based on their unique needs.

Tercyak KP, Goldman P, Smith A, Audrain J: Interacting Effects of Depression and Tobacco Advertising Receptivity on Adolescent Smoking. Journal of Pediatic Psychology 27(2): 145-154, 2002.

Protection Against Persistent Hepatitis C

Background: The high rates and serious consequences of Hepatitis C Virus (HCV), particularly in injecting drug users highlights the importance of developing effective prevention strategies for HCV infection. Immunization efforts against HCV in chimpanzees and the occurrence of re-infection in humans have suggested that vaccination using HCV-derived antigens is unlikely to be successful in eradicating HCV infection. However, the magnitude and duration of viral infection may be affected by prior exposure (or vaccination), which could ultimately lead to improved outcomes regarding cirrhosis and cancer of the liver since these illnesses appear related to persistent HCV infection.

Advance: Researchers identified 98 intravenous (i.v.) drug users who were previously infected with HCV, but no longer showed antibodies to the virus, and 164 i.v. drug users who had no previous HCV infection. Both groups were assessed at 6-month intervals for approximately 2 years to determine the incidence, severity, and duration of HCV infection or reinfection. Although all participants received counseling to reduce drug use and referrals for treatment, many continued to engage in i.v. drug use. Although the group did not differ on drug use during the 2-year period of the study, 12 percent of previously infected drug users became re-infected with HCV compared to 21 percent new infections in the previously uninfected group. Moreover, in those who had prior HCV- infections, lower concentrations of the virus and less persistence were noted compared to newly infected individuals.

Implications: The findings suggest that humans can acquire partial immunity to HCV infection that protects against persistent HCV, which is linked to cirrhosis and cancer of the liver. Moreover, the data from this study along with that from studies in chimpanzees (which show a diminishing viral response to repeated HCV exposures or following vaccination) suggest that the nature of the re-infection with HCV is different from that of initial infection and is characterized by a low level of the virus, which resolves. These results suggest a reconsideration of the development and use of vaccines for HCV in attempt to prevent the morbidity and mortality associated with persistent HCV infection.

Mehta SH, Cox A, Hoover DR, Wang X-H, Mao Q, Ray S, Strathdee SA, Vlahov D, Thomas DL: Protection against persistence of hepatitis C. Lancet, 359: 1478-1483, 2002.

New Clues to Risk for HIV-Dementia

Background: Human immunodeficiency virus type I (HIV-1) infects and depletes specific types of cells that are critical to maintaining a healthy immune system. The virus also damages the central nervous system, with 15 to 25 percent of infected individuals developing dementia and a higher percentage developing encephalitis (brain inflammation). It is unclear exactly how HIV-1 penetrates the brain, but monocytes and macrophages, cells mobilized in response to the infection, attack the virus by making and releasing inflammatory agents such as macrophage chemotactic protein-1 (MCP-1), which can ultimately have toxic effects.

Advance: NIH-sponsored investigators studied macaque monkeys infected with a strain of HIV known as simian immunodeficiency virus (SIV). The researchers determined that SIV causes a temporary increase in the ratio of MCP in cerebral spinal fluid (CSF) to MCP in blood in all monkeys 10 days after infection. Thereafter, in monkeys that do not develop encephalitis, the CSF-to-blood ratio decreases and remains low. In macaques that developed moderate to severe encephalitis, the ratio escalated to much higher levels approximately 28 days after infection. When the macaques' brains were examined 56 days after SIV infection, the researchers found that the increase in the MCP CSF-to-blood ratio occurred before brain inflammation. This finding suggests that this early predictor of brain inflammation could be used to design treatments that, if used in initial stages of infection, might prevent or lessen the development of the inflammation. Additionally, the investigators identified the types of brain cells that appear to be making and releasing the MCP-1 as macrophages and astrocytes.

Implications: The findings indicate that MCP is an excellent candidate marker of early brain infection, and it may also indicate those individuals susceptible to HIV-induced brain inflammation and related complications in humans. Such early predictors could be used to tailor current drug treatment regimens and to develop new drugs that specifically target the brain inflammatory processes for susceptible individuals.

Zink MC, Coleman GD, Mankowski JL, Adams RJ, Tarwater PM, Fox K, Clements JE: Increased macrophage chemoattractant protein-1 in cerebrospinal fluid precedes and predicts simian immunodeficiency virus encephalitis. Journal of Infectious Diseases 184: 1015-1021, 2001.

Diabetes Prevention

Background: Sixteen million people in the United States have diabetes mellitus. This devastating disease has no cure, increases the risk for heart disease and stroke, and shortens life expectancy by 15 years. Diabetes is a complex disease caused by the body's inability to make or use insulin. Type 1 diabetes usually begins in childhood, but may strike at any age. Type 2 diabetes normally affects adults after age 40, but is becoming more common in children, particularly minority children. Type 2 diabetes affects approximately 16 million people in the United States, or about 12 percent of the population between 40 and 74 years of age.

Advance: The Diabetes Prevention Program, a multi-center clinical trial sponsored by the NIH, recently found that lifestyle changes of 150 minutes of physical activity weekly and treatment with metformin both reduced the incidence of type 2 diabetes in persons at high risk. The lifestyle intervention was more effective than metformin with one case of diabetes prevented per seven persons treated for three years.

Implications: The results of this recently conducted large, multi-center, randomized, controlled clinical trial that followed 3,234 patients, 45 percent of which were racial and ethnic minorities, provides proven prevention strategies for delaying the onset and progression of type 2 diabetes.

Knowler WC, Barrett-Connor E, Fowler SE, HammanRF, Lachin JM, Walker EA, Nathan DM: Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346(6): 393-403, 2002.

Cancer Risk Can be Reduced through Surgery in Women with Known Cancer Gene Mutations

Background: The discovery of genes associated with increased susceptibility to cancer is beginning to translate into improved medical practice. Two such genes, known as *BRCA1* and *BRCA2* (breast cancer genes 1 and 2), are much more likely to be altered (mutated) in women who have developed ovarian or breast cancer. Other women who have these mutations have a significantly increased susceptibility to these cancers. Genetic testing to determine a woman's *BRCA* status could thus provide an important measure of her breast and ovarian cancer risk.

Risk assessment tools have been developed to help patients identify and balance all of their known predispositions and risk factors. In consultation with their health care providers, *BRCA* positive women, especially those whose risk of cancer is independently greater because of family history or other factors, may consider prophylactic surgery as a proactive measure to reduce their cancer risk. But such a major decision ideally would be based on evidence that the surgery, which removes the breasts or ovaries, would statistically reduce their risk of developing a cancer. Such evidence is being sought.

Advance: Two recent studies demonstrate the prognostic value of knowing a woman's *BRCA* status in making decisions about surgical interventions to reduce the risk of cancer. The studies were conducted to determine if there was a protective effect for women who elected surgery. One study compared *BRCA* positive women who had both ovaries removed with those who did not. Those who had the surgery cut their breast cancer risk in half, and their risk of ovarian cancer by more than 90 percent. The other study included women who have a family history of breast cancer and who elected to have bilateral prophylactic mastectomy (both breasts removed). About 15 percent of these women were also *BRCA* positive. Previous research indicates that women with an inherited predisposition who undergo this radical surgery can expect a 90 percent reduction in their chances of contracting breast cancer. This study suggests that for the subset of women who are also *BRCA* positive, that number may be even higher.

Implications: Women who are at high risk for developing breast and ovarian cancers may re-evaluate whether to determine if they carry a *BRCA1* or *BRCA2* gene mutation. If they do, the possible value of radical surgical procedures as a preventive measure may be increased. Clearly, however, more research is needed to develop interventions that are less traumatic than the surgical interventions discussed in these studies.

Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Van't Veer L, Garber JE, Evans G, Isaacs C, Daly MB, Matloff E, Olopade OI, Weber BL: Prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations. N Engl J Med 346(21): 1616-1622, 2002.

Hartmann LC, Sellers TA, Schaid DJ, Frank TS, Soderberg CL, Sitta DL, Frost MH, Grant CS, Donohue JH, Woods JE, McDonnell SK, Vockley CW, Deffenbaugh A, Couch FJ, Jenkins RB: Efficacy of bilateral prophylactic mastectomy. Journal of the National Cancer Institute 93(21): 1633-1637, 2001.

Anti-Smoking Interventions Should Target People with Attention Problems and ADHD

Background: Because nicotine helps people concentrate and pay attention, those with attention deficits may be at increased risk of smoking. Studies have shown that even adults who have no attention problems and do not smoke, when given nicotine through a patch on the skin, improve both attention and performance. Those who suffer from Attention-Deficit Hyperactivity Disorder (ADHD) appear more likely to start smoking and have more trouble stopping. Though they may be unaware of it, they are self-medicating to manage their inattention.

The link between nicotine and attention is established, but other complexities make definitive policy recommendations difficult. For example, many people are not diagnosed with ADHD, but may have attention deficits that make them more susceptible to smoking. Considering the lethality of smoking, the modest reductions in smoking initiation achieved among children (especially girls), and the increase in attention problems being observed, the relationship between attention problems and smoking in children and adolescents is of particular concern.

Advance: NIH-funded researchers found that some important smoking behaviors are associated with inattention symptoms, even in people not formally diagnosed with Attention-Deficit Hyperactivity Disorder (ADHD). Their study included 226 male and female smokers aged 18 and older who were enrolled in a program to stop smoking. Though not specifically diagnosed with ADHD, the participants were tested and ranked along scales of the two major symptoms of ADHD, inattention and hyperactivity/impulsiveness. Their smoking patterns were then correlated to these symptoms. No association between smoking behavior and hyperactivity was found, reinforcing earlier study findings. However, those scoring higher on the inattention scale were more likely to smoke, either for stimulation and/or to minimize symptoms of nicotine withdrawal. No gender differences were identified.

Implications: This finding broadens the group of people who could benefit from targeted interventions – either to prevent them from beginning to smoke, or to cope with relapse and/or withdrawal. Scientists have demonstrated that smoking not only causes cancer, but is linked to a number of major health problems and illnesses. Anti-smoking efforts represent a major arm of public health policy. Knowing which people are more susceptible to tobacco use is an important filter for prevention and treatment efforts. This study strongly suggests that people who either have ADHD or who can be identified as having attention problems are at increased risk of smoking.

Lerman C, Audrain J, Tercyak KP, Hawk LW Jr, Bush A, Crystal-Mansour C, Rose C, Niaura R, Epstein LH: Attention-Deficit Hyperactivity Disorder (ADHD) symptoms and smoking patterns among participants in a smoking-cessation program. Nicotine and Tobacco Research 3(4): 353-359, 2001.

Tercyak KP, Lerman C, Audrain J: Association of Attention-Deficit Hyperactivity Disorder (ADHD) symptoms with levels of cigarette smoking in a community sample of adolescents. J Am Acad Child Adolesc Psychiatry 41(7): 799-805, 2002.

Genetic Susceptibility Counseling Accepted in Smoking Cessation Program

Background: Close to one-fourth of all Americans smoke cigarettes and rates are even higher among people with low income and less education. With one in every five deaths in the United States attributable to smoking, it is important that more people quit. Already bearing a disproportionate burden of tobacco-related cancers, African Americans, although they try more frequently, tend to be less successful in quitting smoking and might benefit from smoking cessation interventions.

Advance: Investigators in this NIH-supported effort examined whether feedback about lung cancer susceptibility would help personalize the risks of smoking and motivate people to quit. In addition to standard cessation interventions received by all study participants (mostly low-income African Americans treated at a community health center), some were offered a blood test for a gene that makes a protein to help rid cells of harmful chemicals, like those in tobacco smoke. Those who were missing the gene were told they had a higher risk of lung cancer. People who received genetic feedback were more likely than the others to have quit smoking by six months into the study, but by 12 months there were no longer significant differences between the two groups.

Implications: It is promising that the study participants, predominately low-income, African American smokers, were willing to receive genetic feedback in addition to standard smoking cessation interventions and that short-term quitting rates increased. Further research should test this approach in other populations and optimize the manner of communicating test results to the patients.

McBride CM, Bepler G, Lipkus IM, Lyna P, Samsa G, Albright J, Datta S, Rimer BK: Incorporating Genetic Susceptibility Feedback into a Smoking Cessation Program for African-American Smokers with Low Income Cancer. Epidemiol Biomarkers Prev. 11(6):521-528, 2002.

Several Studies Examine the Effects of Diet on Cancer Risk

Background: Over the years, many studies, small and large, have examined how what we eat or drink can change our risk of developing cancer. Since the information coming out of these studies is sometimes conflicting, there is a need for large cohort studies to clarify some of the findings.

Advance: In several recent studies with tens of thousands of participants, NIH-supported investigators examined how several dietary components affect the risk of developing various cancers. One study demonstrated that multivitamins containing folate, diets high in both folate and methione (found in eggs, meats, and cheese), and avoidance of moderate to heavy alcohol use, may reduce the risk of colon cancer in women who have family history of the disease. Investigators found strong evidence that consuming about 700 mg per day of calcium can reduce the risk of developing cancer of the distal colon in both men and women. In contrast, another study clearly showed that high levels of calcium and dairy products substantially increase the risk for prostate cancer. Lycopene, a component of tomatoes, provides moderate protection against prostate cancer.

Implications: The finding that calcium can reduce the risk of one cancer while increasing the risk of another illustrates the complexity of the interaction between diet and cancer. Further study is needed to define dietary risk factors before clear advice can be communicated to the public.

Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC: A prospective study of tomato products, lycopene, and prostate cancer risk. J Natl Cancer Inst. 94(5): 391-398, 2002.

Fuchs CS, Willett WC, Colditz GA, Hunter DJ, Stampfer MJ, Speizer FE, Giovannucci EL: The influence of folate and multivitamin use on the familial risk of colon cancer in women. Cancer Epidemiol Biomarkers Prev 11(3): 227-234, 2002.

Wu K, Willett WC, Fuchs CS, Colditz GA, Giovannucci EL: Calcium intake and risk of colon cancer in women and men. J Natl Cancer Inst 94(6): 437-446, 2002.

Chan JM, Stampfer MJ, Ma J, Gann PH, Gaziano JM, Giovannucci EL: Dairy products, calcium, and prostate cancer risk in the Physicians' Health Study. Am J Clin Nutr 74(4): 549-554, 2001.

Ovarian Cancer Risk in Women With *BRCA1* and *BRCA2* Genetic Mutations

Background: The risk of non-hereditary ovarian cancer appears to be increased by infertility and giving birth to a small number of children (low parity), and to be decreased by multiparity and use of oral contraceptives. However the impact of a *BRCA1* or *BRCA2* genetic mutation on a woman's risk for ovarian cancer is not known.

Advance: With funding from NIH, researchers recently examined the impact of multiparity and oral contraceptive use on ovarian cancer risk in Israeli women carrying *BRCA1* or *BRCA2* mutations and in noncarriers of these genetic mutations. The researchers tested Jewish women in Israel for two mutations of *BRCA1* and one mutation of *BRCA2* that are known to be common among Jews. They estimated the effects of parity and oral contraceptive use on the risk of ovarian cancer in carriers and noncarriers. The risk of ovarian cancer among carriers of either mutation was found to be decreased with each birth, but not with increased duration of oral contraceptive use.

Implications: These findings suggest that it is premature to consider using oral contraceptives to prevent ovarian cancer in carriers of mutations in the *BRCA1* or *BRCA2* gene.

Modan B, Hartge P, Hirsh-Yechezkel G, Chetrit A, Lubin F, Beller U, et al: Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a *BRCA1* or *BRCA2* mutation. N Engl J Med 345(4): 235-239, 2001.

Hormone Replacement Therapy and Ovarian Cancer Risk

Background: Despite many studies and meta-analyses (analyses of data from several studies), the relationship between hormone replacement therapy (HRT) during menopause and ovarian cancer risk remains unclear. Previous studies have lacked important data on dosage, formulation, and ovarian cancer risk factors. In addition, formulations and dosage regimens have changed over time, making accurate comparisons difficult.

Advance: NIH researchers analyzed 20 years of follow-up data from a large mammography screening study conducted in 29 U.S. screening centers by NIH and the American Cancer Society to assess the impact of estrogen replacement therapy and combined estrogen-progestin replacement therapy on risk of ovarian cancer. Of the 44,241 women studied, 329 developed ovarian cancer during the study period. Use of estrogen replacement therapy was found to be significantly associated with ovarian cancer, regardless of other ovarian cancer risk factors. Women who used estrogen-only replacement therapy for 10 or more years had significantly increased risk of ovarian cancer. Women who used short-term estrogen-progestin replacement therapy were not at increased risk, but these results were based on only 18 women who developed ovarian cancer.

Implications: Further investigation detailing duration, dose, and regimen is needed to determine the ovarian cancer risk associated with short-term and long-term estrogen-progestin hormone replacement therapy.

Lacey JV Jr., Mink PJ, Lubin JH, Sherman ME, Troisi R, Hartge P, et al: Menopausal hormone replacement therapy and risk of ovarian cancer. JAMA 288(3): 334-341, 2002.

Radon Exposure and Lung Cancer Risk in Rural China

Background: Evaluation of lung cancer risk associated with radon in houses in the United States is difficult due to low levels of exposure and residential mobility. Current estimates of this risk have been extrapolated from data on radon exposure among uranium miners.

Advance: To determine the lung cancer risk of residential radon exposures, NIH researchers studied the relationship between radon exposure and lung cancer risk in a rural area of China where indoor radon concentrations are high and residential mobility is low. The researchers examined all lung cancer cases diagnosed between January 1994 and April 1998 in residents aged 30-75 years of two Chinese prefectures, and in their age-, sex-, and prefecture-matched controls. Radon detectors were placed in all houses occupied for 2 or more years during the 5-30 years before study enrollment. Lung cancer risk was shown to increase with increasing radon level.

Implications: These results suggest that high levels of indoor radon increase the lung cancer risk. The effects of residential radon may equal or exceed the estimates of risk currently extrapolated from data on uranium miner exposures.

Wang Z, Lubin JH, Wang L, Zhang S, Boice JD, Cui H, et al: Residential radon and lung cancer risk in a high-exposure area of Gansu Province, China. Am J Epidemiol 155(6): 554-564, 2002.

Tamoxifen and Breast Cancer Risk in Women with Inherited *BRCA* Mutations

Background: In the NIH-sponsored Breast Cancer Prevention Trial (BCPT) conducted from 1992 to 1998, researchers showed that tamoxifen reduced by half the risk of estrogen receptor positive (ER-positive) breast cancer in healthy women aged 35 years or older who were at high risk for the disease. ER-positive cancers retain a receptor for estrogen and grow in the presence of this hormone. Although mutations in the *BRCA1* and *BRCA2* genes are now known to increase breast cancer risk, the genes had not been cloned when the BCPT began. Whether tamoxifen reduces breast cancer risk in healthy women carrying these mutations was therefore unknown.

Advance: At the beginning of the BCPT, women gave blood samples and were randomly assigned to receive either tamoxifen or a placebo. Researchers in the current study examined DNA from blood samples of women who developed invasive breast cancer during the course of the BCPT to determine if they had inherited BRCA1 or BRCA2 mutations. They found that in women with inherited *BRCA2* mutations, tamoxifen reduced breast cancer risk by 62 percent. This was expected, because tumors associated with *BRCA2* mutations retain the estrogen receptor. Researchers did not see an effect for women with inherited *BRCA1* mutations, which generally are associated with tumors that lose the estrogen receptor.

Implications: Tamoxifen is an effective treatment for preventing ER-positive breast cancer in high risk women, regardless of whether these women carry mutations in *BRCA1* or *BRCA2*. The current study shows that tamoxifen may also reduce breast cancer risk in women carrying inherited *BRCA 2* mutations. Larger studies are needed to confirm this result and to determine if earlier tamoxifen use might benefit women with *BRCA1* mutations.

King MC, Wieand S, Hale K, Lee M, Walsh T, Owens K, Tait J, Ford L, Dunn BK, Costantino J, Wickerham L, Wolmark N, Fisher B: Tamoxifen and breast cancer incidence among women with inherited mutations in *BRCA1* and *BRCA2*. JAMA 286(18): 2251-2256, 2001.

COX-2 Inhibitor Reduces Recurrence of Precancerous Polyps in Those with Severe Duodenal Disease

Background: Familial adenomatous polyposis (FAP) is a genetic disease in which carriers have hundreds of polyps throughout the colon. FAP patients often develop cancer in their 30s and almost inevitably in their 40s or 50s if they are not treated. Treatment to date has been surgical removal of parts or all of the colon. FAP patients also have an increased risk of duodenal (small intestine) cancer, and often have duodenal polyps, a precursor to cancer. Previous studies of the COX-2 inhibitor celecoxib in FAP patients showed the drug reduced the numbers of colon polyps, and in 1999 the FDA approved it as an adjunct to usual care.

The cyclooxygenase enzymes COX-1 and COX-2 help create hormones called prostaglandins. COX-1 is needed for healthy mucosal tissue. COX-2 is produced by inflammatory and cancerous tissue, and has been shown to be an early event in adenoma development. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) block both enzymes, but drugs like celecoxib block only COX-2, leaving COX-1 to perform essential tasks.

Advance: A clinical trial involving 83 FAP patients showed a significant reduction in duodenal polyps after six months of treatment twice a day with 400 mg of celecoxib, compared with placebo. This is the first study to show a clinically significant improvement in duodenal polyposis after treatment with celecoxib.

Implications: Celecoxib may offer a new option for treating patients whose FAP disease includes duodenal growths, and it may be useful for patients with duodenal disease, particularly in severe cases.

Phillips RKS, Wallace MH, Lynch PM, Hawk E, Gordon GB, Saunders BP, Wakabayashi N, Shen Y, Zimmerman S, Godio L, Rodrigues-Bigas M, Sue L-K, Sherman J , Kelloff G, Levin B, Steinbach G: A randomised, double-blind, placebo-controlled study of celecoxib in familial adenomatous polyposis. Gut 50: 857-860, 2002.

Pain and Symptoms of Depression in Scleroderma

Background: Scleroderma (systemic sclerosis) is a rare connective tissue disease that can affect multiple organ systems. Some small studies suggest that pain is a problem for people with scleroderma, but little research has examined the frequency or impact of pain in this disorder. This study sought to determine the frequency and impact of pain and symptoms of depression on physical functioning and social adjustment in patients with scleroderma.

Advance: Pain, symptoms of depression, number and variety of social interactions, physical functioning, and social adjustment were studied in 142 scleroderma patients. Sixty-three percent of patients reported at least mild pain and 50 percent reported at least mild levels of depressive symptoms. Pain was the single strongest predictor of physical functioning, and depressive symptoms were the single strongest predictor of social adjustment. These findings indicate that pain is common in scleroderma and that pain and depressive symptoms are significant determinants of physical functioning and social adjustment, two important components of health-related quality of life. Given the frequency and impact of pain in scleroderma, it will be important for future studies to examine the location, quality, and physiological basis of pain in this disease, and to identify appropriate pain management interventions.

Implications: Neither pain nor depressive symptoms need to reach severe levels before affecting function. Careful assessment of such symptoms is important, and patients reporting even mild pain and mild symptoms of depression may benefit from interventions focused on coping with pain and reducing distress. Effective management of pain and depression in scleroderma may lead to improved functioning and quality of life.

Benrud-Larson LM, Haythornthwaite JA, Heinberg LJ, Boling C, Reed J, White B, Wigley FM: The impact of pain and symptoms of depression in scleroderma. Pain 95(3): 267-275, 2002.

Gene Therapy as a Treatment for Wear-Debris Induced Osteolysis

Background: The success of total joint replacement for end-stage arthritis of the hip and knee joints has been frequently documented. Despite this success, the major problem still facing this medical technology is the generation of wear particles from the artificial joint, and the body's reaction to them. This process, which has also been called an inflammatory cascade, or "osteolysis," is literally the disappearance of bone around the implant. This can result in the implant becoming loose, which can lead to mechanical failure, requiring that the joint replacement be re-done.

As this process is not unlike osteoporosis, initial studies in lab animals have shown that current medications to treat osteoporosis (i.e., Alendronate) may be an effective in preventing osteolysis. A new approach involves gene therapy, literally the use of an altered virus, that is injected, which then changes how a cell, tissue, organ or individual functions. A prime element of this "inflammatory cascade" is tumor necrosis factor alpha (TNF-alpha), a naturally occurring chemical in the body. This is the target for many medications (as in osteoporosis) or gene therapy. If you turn off its production you stop the bone loss/osteolysis.

Advance: NIH-supported researchers have previously discovered an animal model to study osteolysis. Using this model, they recently looked at the current state of the art for gene therapy (a family of viruses called adenoviruses), to shut off TNF-alpha production. Surprisingly, they found that the adenovirus vector (i.e., viral injection/delivery vehicle) itself produced a strong reaction, resulting in the disappearance of bone in tested animals.

Implications: These results indicate that adenoviral vectors should not be used for gene therapy for the prevention of osteolysis because of their apparent stimulation of further bone loss. In addition, they call into question the results of adenoviral vectors in other systems because of the strong immune response (i.e., rejection) to this vector. These results do not call into question the target of these vectors (i.e., TNF-alpha), but rather state that other, less immunogenic (i.e., reactive) viral vectors should be chosen.

Childs, LM, et al: Effect of Anti-Tumor Necrosis Factor Alpha Gene Therapy on Wear Debris-Induced Osteolysis, Journal of Bone and Joint Surgery 83-A(12): 1789-1797, 2001.

Adverse Drug Reactions – Genetic Defect Linked to Toxicity of Anticonvulsant Drug

Background: The inability to predict who will have adverse reactions to drugs is a frustrating aspect of devising therapeutic regimes for patients. Understanding the genetic and molecular underpinnings of individual drug responsiveness is a necessary prelude to devising screening programs that can predict people who might have adverse reactions to particular drugs.

A group of liver enzymes, known as cytochrome P450s (CYP) are responsible for metabolizing clinical drugs as well as environmental compounds like pesticides. CYP2C9 is one of the most important of these enzymes. It is responsible for the metabolism of many clinically important drugs such as the anticonvulsant, phenytoin (used for epilepsy); the anticoagulant, warfarin; antidiabetic drugs, such as tolbutamide; and most common nonsteroidal anti-inflammatory drugs such as ibuprofen and Celebrex.

Advance: A new genetic polymorphism was discovered in an African-American individual who was found to be homozygous for a single base pair deletion in the gene coding for CYP2C9 resulting in the complete absence of this enzyme in the liver. As a result, standard recommended doses of drugs like phenytoin and warfarin was dangerous for this individual and for others carrying this trait. A preliminary screen of African-American individuals indicate that 1/60 African-Americans carry at least one gene for this defect. This is the first example of a null polymorphism (completely inactivating defect) in this medically important enzyme. A genetic test was developed for this genetic defect, which can identify an individual carrying this defect from less than a single drop of blood.

Implications: Such genetic tests in the future can lead to individualized medicine in the future, alerting the physician to patients who cannot tolerate normal doses of medicines.

Kidd RS, Curry TB, Gallagher S, Edeki T, Blaisdell J, Goldstein JA: Identification of a new null allele of *CYP2C9* in an African-American exhibiting toxicity to the anticonvulsant drug phenytoin. Pharmacogenetics 11(9): 803-808, 2001.

Fischer T.L, Pieper JA, Graff D W, Rodgers JE, Fischer JD, Parnell KJ, Goldstein JA, Greenwood R, Patterson JH: Evaluation of potential losartin-phenytoin drug interactions in healthy volunteers. Clin Pharmacol Ther72(3): 238-246, 2002.

Potential Improvement for Therapy for Asthma and Bronchitis

Background: The ability to breathe is necessary for life itself. Yet for many people suffering from asthma and bronchitis, breathing can be difficult and painful. In some cases, breathing can be impossible. Each of these conditions is characterized by inflammation of the airways and the production of mucus. Inflammation leads to swelling, and thus reduction, of the airways; mucus production can further restrict air passages. Both conditions are significantly worsened in the presence of air pollutants.

Advance: Scientists have identified the gene responsible for controlling synthesis of inositol 3,4,5,6-tetrakisphosphate, an intracellular signal that regulates a class of chloride ion channels that control salt, fluid and mucus secretion from epithelial cells. These scientists have also discovered how the synthesis of inositol tetrakisphosphate inside cells is tightly coupled to hormone action. As a consequence of these studies, work is now progressing to genetically and pharmacologically manipulate the synthesis of inositol 3,4,5,6-tetrakisphosphate to see to what extent this controls the over-production of airway mucus that results from allergic asthma and bronchitis. This represents a completely novel therapeutic approach to these debilitating pathological conditions.

Implications: These researchers are pursuing this study to determine if therapeutic intervention of inositol 3,4,5,6-tetrakisphosphate synthesis could reduce mucus production and lead to easier breathing for those suffering from bronchitis or asthma attacks.

Ho MWY, Yang X, Carew MA, Zhang T, Hua L, Kwon Y-U, Chung S-K, Adelt S, Vogel G, Riley AM, Potter BVL Shears SB: Regulation of Ins(3,4,5,6)P4 signaling by a reversible kinase/phosphatase. Curr Biol 12: 477-482, 2002.

Drive to Be Thin and Weight Concerns Increase Girls' Risk of Becoming Smokers

Background: Smoking is a preventable risk factor for cardiovascular and respiratory disease. Despite substantial public health efforts, there has been little reduction in smoking rates among adolescents. A better understanding of the environmental, social, and psychological risk factors associated with smoking is needed to help design more effective interventions.

Advance: The study showed that the drive to be thin and concerns about body weight increase the risk that a girl will become a daily smoker by the time she is 18 or 19 years old. The drive for thinness among black girls had not been previously reported. The study found that other factors early in life also increased the risk of later smoking, including stress, having a parent with no formal education beyond high school, being from a one-parent household, drinking alcohol, poor academic performance, and poor conduct. Each factor affected the risk to differing degrees in black and white girls.

Implications: By helping to identify key factors involved in girls' decisions to smoke, the study may lead to more effective smoking prevention strategies. These strategies need to include healthy ways for teenage girls to control their weight and cope with stress. To address the increase in smoking among adolescents, smoking prevention and cessation programs are needed through schools, community venues, and other outlets to target adolescents before they become regular smokers.

Voorhees CC, Schreiber GB, Schumann BC, et al.: Early predictors of daily smoking in young women: The National, Heart, Lung, and Blood Institute Growth and Health Study. Preventive Medicine 34: 616-624, 2002.

Beta-Blockers Protect the Brain During Bypass Surgery

Background: Coronary artery bypass surgery is performed on almost 500,000 patients in the United States each year. Many of them suffer some amount of brain damage after the surgery. Methods of preventing brain injury during bypass surgery are therefore needed to improve the quality of life for patients in the years following surgery.

Advance: A recent study, based on analysis of the medical records of 2,575 patients undergoing cardiac bypass surgery in a single medical center over a 3-year period, found that taking beta-blockers before or during surgery protects the brain and its functions. Results of the study showed that only 3.9 percent of the patients receiving beta-blockers experienced adverse neurological events – comas, strokes, transient ischemic attacks ("mini-strokes"), and cognitive change (specifically, confusion or delirium) – compared with 8.2 percent of those not taking beta-blockers. The analysis took into account a variety of risk factors, such as severity of disease, age, and diabetes.

Implications: Use of beta-blockers constitutes a safe, inexpensive, and effective strategy for averting a debilitating complication of coronary bypass surgery.

Amory DW, Grigore A, Amory JK, et. al.: Neuroprotection is associated with β-adrenergic receptor antagonists during cardiac surgery: evidence from 2,575 patients. Journal of Cardiothoracic and Vascular Anesthesia 16(3): 270-277, 2002.

High-normal Blood Pressure Increases Cardiovascular Risk

Background: High blood pressure (defined as > 140 mm Hg systolic and/or > 90 mm Hg diastolic) is well established as a risk factor for cardiovascular disease. However, less is known about the prognostic significance of high-normal blood pressure (defined as 130-139 mm Hg systolic and/or 85-89 mm Hg diastolic).

Advance: Using data from the Framingham Heart Study, researchers found that persons with high-normal blood pressure had a 1.6 to 2.5 times the risk of suffering a heart attack, stroke, or heart failure in 10 years compared with persons who had optimal blood pressure. The risk was higher for men than for women and increased continuously with age. After 10 years of follow-up, the risk of cardiovascular disease in persons aged 35-64 who had high-normal blood pressure was 4 percent for women and 8 percent for men. In persons aged 65 or older, the risk was 18 percent for women and 25 percent for men.

Implications: The findings support the wisdom of encouraging persons with high-normal blood pressure to undertake lifestyle changes to lower it to a healthier level. This is especially true for older individuals who are likely to have other cardiovascular disease risk factors, such as high cholesterol and diabetes. The data also highlight the need for intervention studies to determine conclusively whether setting a lower target for blood pressure control is warranted.

Vasan RS, Larson MG, Leip EP, et al.: Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 345(18): 1291-1297, 2001.

DASH Diet and Reduced Sodium Lowers Blood Pressure for All

Background: Nonpharmacologic approaches, such as diet, can play an important role in lowering high blood pressure, the chief risk factor for stroke and a major risk factor for heart disease. Researchers previously reported successes in reducing blood pressure with the Dietary Approaches to Stop Hypertension (DASH) diet and/or reduced sodium intake. The DASH diet is rich in fruits, vegetables, and low-fat dairy foods and reduced in total and saturated fat.

Advance: Researchers measured the effects of the DASH diet and reduced sodium intake on blood pressure reduction in various population subgroups. The effects were seen for persons with and without hypertension or a family history of hypertension, older and younger adults, men and women, African-Americans and members of other races, and obese and nonobese people. In addition, the effects occurred among people with higher and lower physical activity levels, larger and smaller waist circumferences, and higher and lower annual family income or education. Researchers found that although the combination of the DASH diet and reduced dietary sodium produced the biggest reductions, each intervention also lowered blood pressure when used alone.

Implications: Based on these findings, all subgroups of the population would benefit from eating the DASH diet and reducing sodium intake in order to lower their high blood pressure, and in turn reduce their risk of stroke and heart disease.

Vollmer WM, Sacks FM, Ard J, et al.: Effects of diet and sodium intake on blood pressure: subgroup analysis of the DASH-sodium trial. Ann Intern Med 135(12): 1019-1028, 2001.

Treatment Helps Patients with Low HDL Cholesterol Levels

Background: Both high blood levels of LDL ("bad") cholesterol and low blood levels of HDL ("good") cholesterol increase risk of developing coronary heart disease. Although much evidence exists to support the benefits of lowering LDL levels, the effects of raising HDL levels or of improving the balance between LDL and HDL levels had not previously been studied thoroughly.

Advance: The HDL Atherosclerosis Treatment Study (HATS), a randomized clinical trial, was designed to evaluate the effect of lowering LDL and raising HDL on the progression of atherosclerosis in coronary disease patients who had normal LDL but low HDL cholesterol levels. Participants were treated with a combination of simvastatin (a statin drug) and niacin or a placebo. The simvastatin-niacin combination was found to be associated not only with a significant reduction in the progression of atherosclerosis, but also with a significant reduction in clinical events such as heart attack, strokes, and deaths.

Implications: The findings from this clinical trial show that treatment with this combination of simvastatin and niacin is well tolerated and efficacious for a specific group of heart patients. These findings add to the growing evidence that even patients without elevated LDL cholesterol levels can benefit from treating low HDL cholesterol levels.

Brown BG, Zhao XQ, Chait A, et. al.: Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 345(22): 1583-1592, 2001.

Consumption of Fish Oil May Help Prevent Sudden Cardiac Death

Background: Approximately 250,000 sudden cardiac deaths occur in the United States each year. Nearly half of the victims have no signs of existing heart disease. Previous studies have suggested that ingestion of fish oil (which contains omega-3 fatty acids) may reduce the incidence of sudden cardiac death.

Advance: Recently published results from two studies provide additional evidence of the benefit of ingestion of fish oil. One study analyzed dietary consumption and follow-up data from 84,688 female nurses enrolled in a long-running epidemiology study. It showed that higher consumption of fish, as well as higher consumption of omega-3 fatty acids, is associated with a lower risk of coronary heart disease, and a lower risk of sudden cardiac death, in particular. The other study examined blood levels of omega-3 fatty acids, rather than fish ingestion, in a group of apparently healthy men who were followed for up to 17 years. It showed an association between high blood levels of omega-3 fatty acids and reduced likelihood of sudden cardiac death.

Implications: These findings suggest that increased consumption of omega-3 fatty acids found in fish oil could be a cost-effective, population-wide approach to preventing sudden cardiac death and may also lead to the development of an improved preventive regimen that combines cholesterol-lowering drugs with increased intake of omega-3 fatty acids. Findings from these and other studies have already led the American Heart Association to recommend that individuals include at least two fish meals per week in their diets.

Hu FB, Bronner L, Willett WC, et al.: Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. JAMA 287(14): 1815-1821, 2002.

Albert CM, Campos H, Stampfer MJ, et al.: Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med 346(15): 1113-1118, 2002.

Existing Supply of Smallpox Vaccine Can Be Expanded to Protect More Americans

Background: One of the nation's highest public health priorities is developing strategies to counter bioterrorism threats from smallpox. The virus that causes smallpox, *Variola major*, is among the most potentially dangerous biological weapons because it spreads easily from person to person, causes severe effects, and has no effective treatment. Few people have full immunity, if any, to the virus anymore because, in the absence of new cases of smallpox, the United States discontinued routine vaccinations three decades ago, and because immunity is thought to wane over time in vaccinated individuals. Although the disease was eradicated worldwide through a successful immunization program, and authorized samples of the virus are stored in only two laboratories in Russia and the United States, unauthorized sources of the virus are believed to exist, increasing the likelihood that smallpox could be intentionally released. If such an emergency should occur, there is an insufficient supply of smallpox vaccine available to adequately vaccinate all U.S. residents with the recommended dose. Thus, it is important to determine whether the current supply of the vaccine could be used in diluted form to increase quickly the available number of doses of the vaccine while still providing effective protection against the smallpox virus.

Advance: Results from an NIH-supported clinical study indicate that the existing U.S. supply of smallpox vaccine – 15.4 million doses – could successfully be diluted at least five times and retain its potency, effectively expanding the number of individuals it could protect from the contagious disease. The study compared the effectiveness of full-strength smallpox vaccine to that of fivefold and tenfold diluted vaccine in 680 adults aged 18 to 32 with no history of smallpox vaccination. More than 97 percent of all participants in the study responded with a vaccine "take," a blister-like sore at the injection site that serves as an indirect measure of the vaccine's effectiveness. Most important, the investigators found no significant difference in the take rate of the three doses.

Implications: In the event of an intentional release of smallpox, the U.S. stockpile of smallpox vaccine could be expanded significantly to protect more people and help contain a potential epidemic. The demonstration that existing supplies of vaccine can be successfully expanded is an important component of the Department of Health and Human Services' bioterrorism preparedness plan, which includes the goal of having enough smallpox vaccine to vaccinate every American in case of a biological attack with the virus. Production of additional doses of the vaccine to supplement existing stores also is under way.

Frey SE, Couch RB, Tacket CO, Treanor JJ, Wolff M, Newman FK, Atmar RL, Edelman R, Nolan CM, Belshe RB: for the National Institute of Allergy and Infectious Diseases Smallpox Vaccine Study Group: Clinical responses to undiluted and diluted smallpox vaccine. N Engl J Med 346(17): 1265-1274, 2002.

Antibody Treatment May Prevent Mother-to-Infant Transmission of HIV

Background: Mother-to-child transmission (MCT) of human immunodeficiency virus (HIV) can occur during pregnancy, during labor and delivery, or after delivery through breastfeeding. Although the frequency of MCT of HIV has been sharply reduced in the United States through voluntary HIV testing and counseling and treatment of HIV-infected pregnant women, the Centers for Disease Control and Prevention estimates that 280 to 370 infants are born with HIV infection each year in the United States. NIH-supported researchers have been working to develop antibody-based treatments to prevent mother-to-child HIV transmission – an approach that is likely to be less toxic than treatment with antiviral drugs. To test this approach, the scientists studied rhesus monkeys infected with a genetically engineered hybrid virus known as simian (monkey) human immunodeficiency virus, SHIV, under conditions that mimic exposure of newborn human babies to HIV during or after delivery. NIH-supported researchers previously showed that they could prevent maternal transmission of SHIV to newborn monkeys by treating the mother before birth (prenatally), and then treating the infant immediately after birth (postnatally), with a combination of three antibodies that react against the human portion of the hybrid SHIV virus.

Advance: NIH-supported researchers assessed the efficacy of post-natal monoclonal antibody treatment of infants. The postnatal treatment of newborns requires fewer antibodies and is thus more cost-effective. Researchers demonstrated that they could prevent transmission of SHIV to newborn rhesus monkeys by treating the newborns with a combination of three virus-neutralizing human monoclonal antibodies given intravenously. In a pilot experiment, the scientists were able to prevent infection with SHIV in two newborn monkeys by treating them with the triple antibody combination on the day they were born and again when they were 8 days old. Immediately after the initial antibody treatment, the monkeys were exposed to the virus by mouth. Four "control" animals that also were exposed to SHIV by mouth but received no antibody treatment became infected with the virus. In a second experiment, in which a more virulent form of SHIV was given by mouth to four antibody-treated newborns and four untreated control animals, the triple antibody treatment prevented infection in only one of the four newborns. Two other newborns that received the antibody treatment showed some signs of diminished disease severity, whereas all the untreated newborns became infected and showed signs of disease.

Implications: The results of this study indicate that, with some refinements, treatment of newborn babies with a combination of antibodies against HIV may play a role in preventing mother-to-child transmission of the virus. This approach, which is likely to be less toxic than antiviral drug therapy, may be useful for protecting babies from being HIV infected from their mother's milk during breastfeeding.

Hofmann-Lehmann R, Vlasak J, Rasmussen RA, Smith BA, Baba TW, Liska V, Ferrantelli F, Montefiori DC, McClure HM, Anderson DC, Bernacky BJ, Rizvi TA, Schmidt R, Hill LR, Keeling ME, Katinger H, Stiegler G, Cavacini LA, Posner MR, Chou TC, Anderson J, Ruprecht RM: Postnatal Passive Immunization of Neonatal Macaques with a Triple Combination of Human Monoclonal Antibodies Against Oral Simian-Human

Immunodeficiency Virus Challenge. J Virol 75(16): 7470-7480, 2001.

A Novel Approach to Block HIV Infection

Background: The widespread use of combinations of antiviral drugs to treat human immunodeficiency virus (HIV) infection has dramatically improved the clinical course for many people infected with HIV. However, there is an urgent need to develop new antiviral drugs due to the toxicities associated with long-term use of the drugs currently used in combination antiviral therapy. One of the key goals is to develop antiviral drugs that can block, or inhibit, the entry of HIV into CD4+ T cells, the immune cells that are the primary target of HIV. Infection of these white blood cells by HIV is a complex, multistep process that starts with attachment of the virus to a CD4 molecule on the outside surface of the cell. The next generation of antiviral drugs may include entry inhibitors that prevent HIV from attaching to CD4+ T cells. Past attempts to develop inhibitors of viral entry have failed, in part because entry inhibitors were unable to efficiently prevent HIV from attaching to the CD4+ T cell. Moreover, at low levels these inhibitors actually enhanced the ability of HIV to infect CD4+ T cells.

Advance: NIH researchers have constructed a compound that inhibits entry of HIV into CD4+ T cells and does not enhance HIV entry under any conditions. This compound is a large protein that binds specifically to the part of the HIV virus that attaches to the CD4+ T cell. This large protein molecule can bind to at least 10 CD4 attachment sites on the HIV virus. When this large protein latches onto HIV, the virus cannot attach to and gain subsequent entry into the CD4+ T cell. The protein exhibited extraordinarily strong binding to HIV, and the binding appeared to be almost irreversible. As a result, relatively small amounts of this protein were able to neutralize HIV samples from a broad range of infected patients. This represents a 1,000-fold increase in inhibitory activity relative to previously tested CD4-based entry inhibitors.

Implications: The results of this study provide researchers with information on the properties needed in a drug that can effectively prevent HIV entry into CD4+ T cells and does not have the unintended and undesirable effect of enhancing the ability of HIV to infect these cells. This information should aid in the design of more effective drugs for the treatment of HIV infection and lead to novel approaches in vaccine growth.

Arthos J, Cicala C, Steenbeke TD, Chun T-W, Cruz CD, Hanback DB, Khazanie P, Nam D, Schuck P, Selig SM, Van Ryk D, Chaikin MA, Fauci AS: Biochemical and biological characterization of a dodecameric CD4-Ig fusion protein. J Biol Chem 277(13): 11456-11464, 2002.

Half-Dose Flu Vaccine -An Alternative for Healthy Adults During Vaccine Shortages

Background: Millions of people in the United States – about 10 to 20 percent of U.S. residents – will get influenza (the flu virus) each year. Winter flu epidemics are associated with an average of about 20,000 deaths and 114,000 hospitalizations per year in the United States. Much of the illness and death caused by influenza can be prevented by an annual vaccination. However, in 2000, there were concerns about the possibility of a substantial shortage of influenza vaccine. NIH rapidly responded by implementing a clinical trial at six U.S. academic medical centers to test whether giving a half dose of influenza vaccine to healthy adults would give the same anti-influenza immune response as a full dose.

Advance: NIH-supported researchers vaccinated approximately 1,000 healthy adults aged 18 to 49 with either a half dose or the full dose of the 2000-2001 winter season influenza vaccine. The researchers then compared blood samples taken from study participants before and 21 days after vaccination. To assess the level of protection conferred by the vaccines, the researchers measured the levels of antibodies that developed in the blood in response to each of the three inactive flu virus strains contained in the vaccine. They found that the antibody response for all three strains was lower, on average, in those people who received a half dose compared to those who received the full dose. However, the differences in response to the two doses were small for all three strains of the virus. In addition, there was no significant difference in the reporting of complaints or adverse symptoms due to vaccination between the two groups.

Implications: These results suggest that administering a half dose of flu vaccine to healthy adults could increase the number of people vaccinated with relatively little adverse impact on the vaccine's ability to generate an immune response and protect against infection. Although a full dose of influenza vaccine is still recommended, the results of this study show that giving a half dose may be an alternative strategy for protecting healthy adults in an emergency situation when the vaccine supply is substantially limited.

Treanor J, Keitel W, Belshe R, Campbell J, Schiff G, Zangwill K, Wolff M, Klimov A, Levandowski R, Lambert L: Evaluation of a single dose of half strength inactivated influenza vaccine in healthy adults. Vaccine 20: 1099-1105, 2002.

Refining Tissue Typing May Lead to More Successful Bone Marrow Transplantations

Background: Adult stem cells found in the bone marrow (the soft tissue inside bones) replenish the body's supply of essential blood cells – red blood cells, platelets, and white blood cells. People with disease of the blood cells, such as leukemia, often require high doses of chemotherapy or radiation to destroy the cancer cells, but this treatment kills the healthy blood cells as well. The destruction of these blood cells is life threatening unless the patient receives a fresh supply of the blood stem cells through bone marrow transplantation. It is important that the transplanted cells match the recipient's cells as closely as possible to decrease the chance of rejection. Studies have shown that successful transplantation of these cells is influenced by differences in certain types of genes known as HLA-A, B, and C that are found in the donor and the recipient. Studies have shown that mismatches of HLA (human leukocyte antigens) between the donor and the recipient increase the risk of graft failure after bone marrow transplantation. To help determine the success of transplanting tissue, a procedure called HLA typing is performed to ascertain how well the HLA of the donor's marrow match the HLA of the recipient's marrow. HLA typing is performed by using two methods: DNA analysis of the HLA genes, called HLA allele typing, or the more commonly-used antibody recognition of HLA molecules method called HLA antigen typing.

Advance: In the first large comparative study of the two typing methods, NIH-supported investigators tested the hypothesis that allele mismatches, which are detectable only at the DNA level, are associated with a lower risk of bone marrow graft failure than antigen mismatches. HLA typings were performed to identify the HLA-A, B, and C alleles and antigens in 471 patients who received bone marrow from unrelated donors for the treatment of chronic myeloid leukemia. Results showed that a single allele mismatch did not increase the risk of graft failure, whereas a single antigen mismatch significantly increased the risk. Investigators also found that two allelic mismatches present an increased risk that is comparable to a single HLA antigen mismatch and that some HLA antigenic mismatches present more risk than others.

Implications: These results suggest that DNA differences that are undetectable by conventional antigen typing are risk factors for graft rejection and emphasize the importance of DNA-based HLA typing to help researchers find a way to achieve better outcomes for bone marrow transplant recipients. In addition, the finding that a single allele mismatch does not increase risk of graft failure should significantly increase the number of "matched" bone marrow donors available for a recipient. Together, these finding may lead to significant improvements in the numbers of successful bone marrow transplantation.

Petersdorf EW, Hansen JA, Martin PJ, Woolfrey A, Malkki M, Gooley T, Storer B, Mickelson E, Smith A, Anasetti C: Major-histocompatibility-complex Class I alleles and antigens in hematopoietic-cell transplantation. N Engl J Med 345(25): 1794-1800, 2001.

Experimental AIDS Vaccine Protects Monkeys from Disease

Background: Recent efforts to develop a vaccine to prevent human immunodeficiency virus (HIV) infection or Acquired Immunodeficiency Syndrome (AIDS) have emphasized approaches that stimulate a strong cellular immune response because these responses correlate well with nonprogression to AIDS in HIV-infected people and the control of viral replication. The cellular immune response consists primarily of cytotoxic lymphocytes, or "killer" T cells – white blood cells that attack cells infected with a virus. The other main type of immune response that can control foreign invaders, such as viruses, involves neutralizing antibodies that circulate in body fluids and inactivate the virus or prevent it from infecting cells. Live attenuated (weakened) viruses are often used as vaccines (for example, for polio, measles, and mumps) because they can no longer produce disease but still stimulate a strong immune response that protects against disease-causing forms of the virus. Although live attenuated HIV could be an effective AIDS vaccine, scientists are concerned about the risk of disease in response to immunization with even a weakened form of HIV. As an alternative approach, some scientists have been investigating vaccines that use a live attenuated animal virus called vesicular stomatitis virus (VSV) as a "vector," or carrier, for HIV genes. VSV-based vaccines have been effective in animal models, can be given without injection, and stimulate strong cellular and antibody immune responses.

Advance: NIH-supported researchers recently developed a vaccine that effectively prevented AIDS from developing in rhesus macaque monkeys that were exposed to a highly virulent strain of simian (monkey)–human immunodeficiency virus (SHIV), a genetically engineered hybrid virus that mimics HIV infection and causes serious disease in macaque monkeys. The vaccine is based on a form of live attenuated VSV that is genetically engineered to include two genes, *env* and *gag*, from SHIV. This recombinant VSV (rVSV) produces the Gag and Env proteins from SHIV and is thus expected to trigger an immune response to SHIV in vaccinated animals. Seven rhesus macaque monkeys were vaccinated with the rVSV and subsequently exposed intravenously to SHIV. All seven monkeys were protected from disease for up to 2 years after exposure to the virus. The protection from AIDS correlated with both increased antibody levels and cellular immune responses. By contrast, seven out of eight animals that did not receive the vaccine and were exposed to HIV developed AIDS. The VSV-based vaccines showed no adverse effects when given as drops in the nose or mouth or injected into a muscle.

Implications: The results of these animal studies suggest that genetically engineered, live attenuated VSV containing the HIV *gag* and *env* genes, and perhaps other HIV genes, could be used in developing an effective HIV vaccine in humans. Vaccines based on live attenuated VSV are particularly attractive because they can be prepared easily and can be given as a nasal spray or drops, which would facilitate their use on a global scale. These results strongly support testing such vaccines in early human HIV vaccine clinical trials. Testing in humans will be required to establish both safety and potential effectiveness.

Rose NF, Marx PA, Luckay A, Nixon DF, Moretto WJ, Donahoe SM, Montefiori D, Roberts A, Buonocore L, Rose JK: An effective AIDS vaccine based on live attenuated vesicular stomatitis virus recombinants. Cell 106: 539-549, 2001.

Aerobic Exercise Can Reduce Body Fat and Blood Pressure Gains in Adolescents

Background: From 1991 to the year 2000, the prevalence of obesity increased by 61 percent. By the year 2000, 49 states fell within the highest two categories of obesity (27 states had 15 to 19 percent obesity and 22 states had a population ratio of 20 percent obesity or more). Obesity costs totaled $99.2 billion in 1990. The prevalent, long-term health problems of obesity and hypertension are usually associated with adults, but their origins can often be traced to habits that begin in childhood. In addition, coronary artery disease risk factors among youths may be higher in African-Americans than in whites. While regular aerobic exercise can reduce both weight and blood pressure in all age groups, children in regular elementary school physical education (PE) classes spend only 6 percent of their time in aerobic activity, and middle school youths only receive six to ten minutes of exercise in a typical forty minute physical education class. However, interventions to improve physical education classes offer an opportunity to instill regular exercise habits and to educate students about nutrition, weight control, and the benefits of physical activity.

Advance: As part of the Cardiovascular Health in Children and Youth Study (CHIC II), a nurse investigator team tested three interventions as part of a regular middle school physical education program. Schools selected to receive the interventions were primarily rural, with a high proportion of African-American students. The interventions were given as part of an eight-week physical education course. One intervention emphasized exercise only, and involved thirty minutes of aerobic exercise three days per week. The second intervention consisted of two classroom sessions per week on nutrition, smoking, and exercise. The third intervention combined the exercise and education courses. Students in the control group continued in their regular health and physical education curriculum. While some increase in weight, body fat, and blood pressure would be expected due to normal maturation, skinfold measures for body fat increased less in the exercise groups, and blood pressure increased less in all of the intervention groups, compared to the control group. Students in the combined program also improved their exercise capacity.

Implications: Results from this time-limited, eight-week course show that exercise can help control weight and blood pressure even in adolescents. Other studies have shown that exercise should be included in any program to reduce or control hypertension. Regular exercise can moderate the action of the sympathetic nervous system and the renin-angiotensin hormone system, leading to decreased resistance in the peripheral blood vessels. While education on the benefits of proper nutrition and activity is important, regular exercise is needed to effect health changes. Given the potential long-term consequences of obesity and hypertension, implementing a regular and consistent aerobic exercise program for school-age children can help reduce a variety of health risks. Encouraging and establishing healthy habits early on can bring a lifetime of health benefits.

McMurray RG, Harrell JS, Bangdiwala SI, Bradley CB, Deng S, et al: A school-based intervention can reduce body fat and blood pressure in young adolescents. Journal of Adolescent Health 31:125-132, 2002.

Active Lifestyle Generates New Neurons in Aged Brains

Background: Human studies suggest that a mentally and physically active lifestyle gives some protection against developing dementia and neurodegenerative disorders. The biological basis of this effect, however, is not known. Studies using mice demonstrate that physical activity, learning activity, or exposure to an enriched environment causes an increase in the generation of new neurons in the hippocampus, a brain area important for learning and memory, along with an improvement in behavioral performance. The generation of new neurons, termed neurogenesis, is low in aged animals compared to young ones, but can be increased in aged mice by exposure to an enriched environment. These studies indicate that the aging brain retains the potential for change or adaptability in response to experience or activity ("cellular plasticity"). Is it possible that this ability contributes to the beneficial effects of leading an active lifestyle on brain function and pathology? A recent report examines this question.

Advance: In this study, middle-aged (10 months old) mice were housed in either standard, bare cages or in an 'enriched' environment consisting of larger cages with a running wheel, plastic tubes and other play objects. Ten months later, the brains of the now elderly mice (20 months old) were examined for the presence of new neurons in the hippocampal region. Mice living in an enriched environment showed a fivefold higher level of neurogenesis in the hippocampus than control mice, and showed improvements of learning, exploratory behavior, and motor activity. The enriched mice also showed fewer lipofuscin deposits, an age-related indicator of neural degeneration, in hippocampal neurons. Thus, the hippocampus of enriched aged mice appears to be more "healthy" in terms of both degeneration (decreased lipofuscin) and regeneration (new neurons).

Implications: Increased physical and mental activity, even when started in middle age, can enhance hippocampal neurogenesis and decrease signs of neuronal aging in mice. This suggests that neurogenesis might be one factor underlying the beneficial effects of an active lifestyle on brain integrity and cognitive function as suggested for humans. The finding that the adult hippocampus maintains the potential for cellular plasticity, which can be sustained by experience and activity, might be exploited in the development of new prevention and treatment regimens for chronic neurodegenerative disorders, such as Alzheimer's disease, as well as for normal functional changes associated with aging.

Kempermann G, Gast D, Gage FH: Neuroplasticity in old age: Sustained fivefold induction of hippocampal neurogenesis by long-term environment enrichment. Ann Neurol 52(2): 135-143, 2002.

Lifestyle Change and Medication Can Prevent Type 2 Diabetes, but Efficacy of These Interventions May Vary by Age

Background: Diabetes is one of the major debilitating diseases that affect older people. Among the elderly, type 2 diabetes is the most common; it occurs when pancreatic beta cells produce insufficient insulin or when the body cannot use its insulin efficiently. Complications from diabetes can be severe and can include heart disease, eye and nerve damage, stroke, and kidney failure. However, some risk factors for type 2 diabetes, including being overweight and maintaining a sedentary lifestyle, are treatable.

Advance: The NIH has sponsored the Diabetes Prevention Program (DPP), a major, multi-site study. This clinical trial yielded important results for the elderly. The goal of the DPP was to identify interventions that could prevent or delay the development of type 2 diabetes. In this study, over 3,200 men and women, ages 25-85, who were considered "high-risk" based on body mass and blood sugar readings, were randomly assigned to receive one of three interventions: intensive lifestyle intervention, treatment with metformin, and standard medical advice. The lifestyle intervention targeted a 7 percent (or an approximate 15 pound) weight loss and 150 minutes of walking or other moderate-intensity exercise per week. Nearly half of the study participants were members of racial and ethnic groups that suffer disproportionately from type 2 diabetes, including African Americans, Hispanic Americans, Asian Americans and Pacific Islanders, and American Indians. The researchers found that the lifestyle changes reduced by 58 percent the risk of developing type 2 diabetes among all participants. This intervention worked particularly well in people age 60 and older – a group having a nearly 20 percent prevalence of diabetes and who constituted 20 percent of the study population – reducing the development of diabetes by 71 percent in this subgroup. Treatment with the drug metformin also reduced diabetes risk among study participants, but for unknown reasons was less effective among older participants.

Implications: Lifestyle changes and treatment with metformin both appear to be effective in reducing risk of type 2 diabetes among individuals at high risk. The surprising finding was that the lifestyle intervention was most effective among older participants and metformin was less effective in this group. Because the risk of type 2 diabetes increases with age, the finding that modest dietary and physical activity changes can markedly prevent type 2 diabetes can have a major impact on this disease in the elderly. This finding also highlights the importance of ensuring adequate participation of older individuals in clinical studies.

Diabetes Prevention Program Research Group. Reduction in the Incidence of Type 2 Diabetes with Lifestyle Intervention or Metformin. N Engl J Med 346(6): 393-403, 2002.

High Level of Plasma Homocysteine is a Strong Risk factor for Dementia and Alzheimer's Disease

Background: There is a great deal of interest in finding risk and preventative factors for dementia and Alzheimer's disease. Of particular interest are those factors that are modifiable, because intervening with a treatment that can decrease the effect of a risk factor could delay the onset of the disease or even prevent it altogether. This study provides evidence for high levels of the amino acid homocysteine as a modifiable risk factor.

Advance: Investigators followed 1,092 people, average age 76, who enrolled in the study between 1976 and 1978 and who were free of dementia at that time. The participants' plasma homocysteine levels were measured between 1979 and 1982 and again between 1986 and 1990. From the 1986-1990 examinations through December 2000, 111 participants developed dementia, including 83 diagnosed specifically with AD. Elevated homocysteine levels (defined as greater than 14 μmol/liter) doubled the chance that a participant would develop AD and each 5 μmol/liter elevation increased the risk of AD by 40 percent. The analysis showed further that people with consistently high levels of homocysteine throughout the period of the study were at highest risk for dementia and AD. The researchers also examined whether the earlier levels of homocysteine, measured between 1979 and 1982, had any relationship to the development of dementia or AD later on; this analysis, too, linked elevated levels at least 8 years prior to a later diagnosis of dementia and AD. The association between homocysteine and AD was found to be strong and independent of other factors, such as age, gender, APOE genotype, and other known or suspected risk factors for dementia and AD.

Implications: These findings are the first to tie homocysteine levels measured several years before with later diagnosis of AD and other dementias, providing some of the most powerful evidence yet of an association between high plasma homocysteine and later significant memory loss, and indicate a potential risk factor for AD that is modifiable. Blood levels of homocysteine can be reduced, for example, by increasing intake of folic acid (or folate) and vitamins B6 and B12. The therapeutic use of these compounds is being explored in ongoing and planned clinical trials for the treatment and prevention of cognitive decline and Alzheimer's disease.

Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PW, Wolf PA: Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 346(7): 476-483, 2002.

Vaccine Prevents Stroke in Rats

Background: Stroke is the third leading cause of death in the United States and a major cause of serious neurological disability, affecting more than 4 million people. A stroke, or "brain attack," occurs when blood flow to part of the brain is suddenly blocked (ischemic stroke) or when a blood vessel in the brain ruptures, causing bleeding into the brain (hemorrhagic stroke). The U.S. Centers for Disease Control and Prevention estimates that the age-standardized death rate from stroke declined by 70 percent for the U.S. population from 1950 to 1996 [*MMWR Weekly* 48:649-56 1999], and the American Heart Association tallies a 15 percent decline just from 1988 to 1998. This progress reflects the efforts of the NIH, as well as private groups, such as the American Heart Association, with whom we work closely, to prevent stroke through drugs, surgery, and lifestyle approaches. However, because the likelihood of stroke increases with age, and the American population is aging, the number of strokes is increasing, so further progress in stroke prevention is essential.

At blood vessels feeding the brain, inflammatory and immune reactions can trigger both ischemic and hemorrhagic strokes. Relying upon the remarkable advances in understanding the signaling molecules that control the immune system, scientists have begun to work out the critical signaling molecules that control inflammation and to identify potential targets for intervention. E-selectin, for example, is a glycoprotein (a combination of sugars and protein) that occurs on the surface of cells in blood vessels. This molecule plays an important role in inflammatory processes that can lead to stroke, such as mediating the adhesion of various white blood cells to blood vessel walls.

Advance: A new study has developed a vaccine that interferes with a critical step in inflammation inside blood vessels and greatly reduces the frequency and severity of strokes in a strain of hypertensive, stroke-prone rats. The scientists administered a nasal spray containing E-selectin, which programmed white blood cells to monitor blood vessel linings for this protein, and thus for inflammation. On detecting the molecule, the lymphocytes released substances that suppress inflammation. The vaccine procedure potently prevented both ischemic and hemorrhagic strokes. A single dose conferred tolerance that lasted for a period of weeks, and a series of boosters produced a longer-term effect. The effects of the booster procedure reduced both the number of strokes and the average size of strokes that did occur by several-fold.

Implications: Planning is underway for a Phase I trial of this E-selectin approach in people at high risk for stroke. More generally, these findings reinforce the importance of the immune system and inflamation in stroke and support the idea that vaccines, or other ways to modulate the immune system, may be a useful strategy for preventing stroke.

Takeda, H, Spatz M, Ruetzler C, McCarron R, Becker K, Hallenbeck J: Induction of mucosal tolerance to E. selectin prevents ischemic and hemorrhagic stroke in spontaneously hypertensive genetically stroke-prone rats. Stroke 33: 2156-2164, 2002.

Warfarin and Aspirin Effective in the Prevention of Recurrent Stroke

Background: Ischemic stroke is the third leading cause of death in the United States, and a leading cause of long-term disability. For many years, aspirin – a platelet anti-aggregating agent – has been used to prevent recurrent ischemic stroke in individuals with a history of this form of stroke. However, studies in the 1980s and 1990s confirmed the effectiveness of warfarin in preventing first and recurrent strokes in individuals with atrial fibrillation – a condition characterized by an irregular heart rate and rhythm. Although warfarin and aspirin both reduce clotting in the blood, warfarin acts on clotting proteins rather than on the platelets. Despite the effectiveness of aspirin in preventing recurrent stroke in some individuals, the success of warfarin in preventing its recurrence in people with cardiac risk factors led many in the field to believe it might also be superior for preventing recurrent stroke in individuals without these risk factors. However, warfarin is considerably more expensive than aspirin, is costly and time-consuming to monitor, and can cause severe side effects – including brain hemorrhage. For these reasons, it was critical for researchers to conduct a direct comparison of the two compounds in individuals with a history of non-cardiogenic stroke.

Advance: In an effort to resolve this issue, NIH supported a randomized, double-blind, clinical trial that compared the effectiveness of warfarin vs. aspirin in preventing recurrent stroke in individuals with a history of non-cardiogenic ischemic stroke. Over two thousand subjects participated in this study, with half assigned to treatment of warfarin, and half assigned to aspirin. After a two-year follow-up, the results indicated that there was no significant difference in the prevention of recurrent ischemic stroke or death, or in the rate of major hemorrhage, in the two treatment groups.

Implications: This study is the largest trial to date comparing aspirin and warfarin for the prevention of recurrent stroke. The results of this trial are likely to have a significant impact on informing physicians about the most effective medications to use for stroke prevention. In cases where atrial fibrillation is a risk factor, warfarin may be the superior choice. However, when cardiac risk factors are not present, aspirin appears to be as effective as warfarin. Given the lower cost of aspirin, and the ease of its administration compared to warfarin, it will likely be a cost-effective prevention method for many at-risk individuals.

Mohr, JP, Thompson, JLP, Lazar, RM, Levin, B, et al: A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. New Engl J Med 345(20): 1444-1451, 2001.

Prevention of Urinary Tract Infections in Persons With Spinal Cord Injury

Background: According to the National Spinal Cord Injury Statistical Center, approximately 11,000 new cases of spinal cord injury (SCI) occur each year in the United States, and between 183,000 and 230,000 people are currently living with SCI in the U.S. People living with SCI frequently experience urinary tract infections (UTIs) because they need to rely on internal bladder catheters for urine drainage. Because serious health problems and high costs are associated with UTIs, preventing these infections is very important. One of the most common treatments for UTIs is use of antimicrobial agents. However, this therapy has yielded conflicting or disappointing results. Furthermore, using antimicrobial agents in patients with repeat infections increases the likelihood of creating drug-resistant bacteria. Recent studies suggest that intentionally colonizing the bladder with certain harmless bacteria (an approach known as bacterial interference) may help prevent UTIs.

Advance: Researchers inoculated the bladders of individuals, who had a spinal cord injury and frequent episodes of UTI, with a specially engineered bacterial strain *E. coli 83972*. This harmless bacteria proliferated in high concentrations in the bladders of treated individuals and frequently prevented other, more harmful organisms from colonizing there. The rate of UTI was 33 times lower in the 30 patients successfully colonized with *E. coli 83972* than in the group of 14 patients who were not successfully colonized.

Implications: Intentional introduction of harmless bacteria, such as *E. coli 83972,* into the bladders of individuals with SCI may be a safe and effective approach for preventing UTI. The knowledge gained from this study may eventually benefit many people who have disorders that prevent or restrict body movement and who require bladder catheters for urinary drainage. These persons include SCI patients, children with spina bifida, stroke victims, and many nursing home residents. This study could lead to simple, low-cost prevention of the significant health problems associated with UTIs.

Darouiche RO, Donovan WH, Del Terzo M, Thornby JI, Rudy DC, Hull RA: Pilot trial of bacterial interference for preventing urinary tract infection. Urology 58(3): 339-344, 2001.

Parental Influence and Public Policy Can Reduce Teen Driving Risk

Background: Many adolescents attach great importance to the privilege of operating a motor vehicle, but that privilege can have major implications for their social development and health. According to the National Highway Traffic Safety Administration, motor vehicle crashes (MVCs) are the leading cause of death and disability among adolescents 16 to 20 years old. In 1999 approximately 3,560 adolescents were killed in MVCs and an additional 362,000 were injured. Although adolescent drivers represent less than 7 percent of licensed drivers in the United States, they represent more than 14 percent of the drivers involved in fatal crashes. School-based driver education programs have not been shown to be effective at reducing adolescent MVCs, but graduated driver-licensing programs, which impose restrictions on when teens are licensed and under what conditions they may drive, have been shown to reduce MVC risk for young drivers. Parents can extend the benefits of State restrictions by developing and implementing their own tailored family policies on adolescent driving. Unfortunately, parents of adolescent drivers often may not be aware of the need to do so and fail to impose effective driving restrictions on their teens.

Advance: Researchers analyzed adolescent driving risk, the advantages of graduated driver-licensing systems, and the potential for family-oriented programs to moderate adolescent driving risk. Analysis showed that: 1) risk factors that contribute to MVCs among adolescents are young age, lack of driving experience, and high-risk driving conditions; 2) that graduated driver-licensing systems are effective in reducing adolescent MVCs; 3) that parents are in a prime position to influence their adolescents' driving behaviors, but are less involved than they could be; and 4) that instructional materials for parents on how to teach and manage young drivers are available but not universally evaluated or incorporated into comprehensive programs. Despite the adoption of appropriate policies by most states, this analysis found that no jurisdiction contains all the elements of an optimal graduated driver-licensing system as proposed by the Insurance Institute for Highway Safety.

Implications: Mounting evidence suggests that restricting teen driving, as well as the conditions under which teens drive, can reduce high rates of MVCs among young drivers. Graduated driver-licensing programs have been effective where adopted and strong public support exists for such programs. Graduated driver-licensing programs increase parents' perceived empowerment to restrict their teens' driving privileges. The next step will be to develop and test the effectiveness of family-based education programs to promote increased parental management of teen driving.

Beck KH, Hartos J, Simons-Morton B: Teen driving risk: the promise of parental influence and public policy. Health Education and Behavior 29(1): 73-84, 2002.

Oral Diabetes Drug Shows Promise in Preventing Miscarriage inCommon Infertility Disorder

Background: Polycystic ovarian syndrome (PCOS) affects between 5 and 10 percent of American women. PCOS is a condition in which a woman's ovaries become enlarged and filled with cysts due to abnormal ovarian follicle maturation. During normal ovulation, a hormone is released that causes the rupture of one (or sometimes more) mature ovarian follicle. The ruptured follicle releases a mature egg in preparation for reproduction. In women with PCOS, the ovarian follicles fail to mature, are unable to rupture, and become small cyst-like structures. As these cysts accumulate, the ovaries enlarge. Polycystic ovaries are two to five times larger than normal ovaries and they have a very tough white outer covering. Women with PCOS also may experience increased facial and body hair, irregular menstrual cycles, and difficulty getting pregnant. Women who do achieve pregnancy are faced with an increased risk of miscarriage during the first trimester. Women with PCOS also experience insulin resistance. In the past, researchers found that metformin, a drug commonly used to treat non-insulin-dependent diabetes, was successful in treating some of the symptoms of PCOS. A recent study suggests that insulin resistance may be a risk factor for early miscarriage in women with PCOS. Metformin works to increase the body's sensitivity to insulin. Researchers hoped that decreasing insulin resistance would reduce the rate of miscarriage in women with PCOS.

Advance: Researchers compared the pregnancy success rate of two groups of women with PCOS. One group of 65 women received metformin, while a control group of 31 women did not receive the drug. The researchers found that giving metformin to women before and during pregnancy reduced first-trimester miscarriage in women with PCOS. Just over 8 percent of the group receiving treatment with metformin miscarried, compared with almost 42 percent of the women in the control group.

Implications: This research shows that treating women who have PCOS with metformin may reduce the likelihood of a miscarriage. However, more research is needed to confirm the findings. Next, the researchers will need to repeat the trial with a larger number of women. Furthermore, researchers need to evaluate the safety of metformin beyond the first-trimester, throughout pregnancy. Although metformin cannot yet be recommended for reducing the miscarriage risk in women with PCOS, it offers hope as a potential intervention.

Jakubowicz DJ, Iuorno MJ, Jakubowicz S, Roberts KA, Nestler JE: Effects of metformin on early pregnancy loss in the polycystic ovary syndrome. J Clin Endocrinol Metab 87(2): 524-529, 2002.

Epidermal Growth Factor is a Potential Treatment for Necrotizing Enterocolitis

Background: Necrotizing enterocolitis (NEC) is the most common gastrointestinal disorder of prematurely born infants. Every year several thousand premature infants die from NEC in the United States. There is no known cure and there is no known preventive therapy. Treatment for this disease is only supportive. Previously, researchers had designed experimental animal models to study the causes of NEC, which has aided researchers in studying this condition.

Mother's milk seems to reduce the risk of NEC. Researchers have hypothesized that epidermal growth factor (EGF), one of the constituents of mother's milk, might act to prevent NEC. Breast milk is the major source of EGF for newborns. EGF also appears to promote healing of damaged tissue that lines the gastrointestinal tract.

Advance: Researchers fed newborn rats exclusively with either a rat milk substitute that lacked EGF or with the same formula containing EGF. To serve as controls, a third set of newborn rats was allowed to feed normally from their mothers. The researchers induced NEC by exposing the newborn rats to one minute of oxygen deprivation and ten minutes of cold stress twice daily. This treatment simulates the most common conditions for NEC in humans: formula feeding, an immature gastrointestinal tract, and hypoxia (insufficient oxygen supply to tissues). At four days, all animals were examined for the onset of NEC. The researchers found that formula with EGF supplementation reduced the incidence of NEC from 81 percent to 30 percent. None of the mother-fed rats developed NEC. Mother rat's milk contains EGF.

Implications: Although this research was performed in an animal model, the findings seem promising enough to consider clinical studies in premature human infants. The findings of this animal-model experiment also offer hope for using EGF to stimulate the intestinal repair processes in a variety of gastrointestinal disorders, and that milk-borne EGF could play a critical role in maintaining a healthy gastrointestinal track and in healthy development in infants.

Dvorak B, Halpern M, Holubec H, Williams CS, McWilliam DL, Dominguez JA, Stepankova R, Payne CM, McCuskey RS: Epidermal growth factor reduces the development of necrotizing enterocolitis in a neonatal rat model. Am J Physiol Gastrointest Liver Physiol 282: G156-64, 2002.

Odorant Receptors Help Mosquitoes Smell Their Prey

Background: The ability to sense and discriminate chemical clues is important for the behavior of insects. For instance, the sense of smell (olfaction) plays an important role for blood-feeding female mosquitoes in finding a host. Mosquito-borne disease is a serious world health concern and the anopheline mosquito is known to transmit a variety of deadly diseases, including malaria, dengue and yellow fever. Host preference, especially to humans, in the female mosquito is a critical component of disease transmission. A molecular analysis of the mosquito olfactory system may provide opportunities for reducing disease transmission by this insect.

Advance: NIH-supported scientists are characterizing the genes that play a role in the function of the *Anopheles gambiae* olfactory system and have identified odorant receptor-encoding genes selectively turned on in the olfactory organs of this malaria-transmitting mosquito. The scientists cloned four odorant receptor genes (AgOr1-4) from the mosquito and noticed a similarity to the olfactory receptor genes of the fruit fly, *D. melanogaster*. An analysis of the mosquito genes demonstrated no similarities between AgOr3 and AgOr4 and the fly chemosensory receptor genes, suggesting a unique class of mosquito receptors that are associated with olfactory-driven behaviors of this insect. Blood-feeding and host preference selection involve only the female mosquito, so the scientists studied the expression of the AgOr genes in the female mosquito's olfactory tissue. AgOr1 alone is expressed in female olfactory tissue, while AgOr3-4 are found in both male and female olfactory tissues. In addition, it was observed that AgOr1 is turned off in the olfactory tissue of the female mosquito 12 hours after a blood meal, which is consistent with decreased host-seeking behavior.

Implications: These findings suggest that AgOr1 may act as a defector of an olfactory signal that is active in female mosquitoes before but not after a blood meal. Modification of this gene may serve to control the transmission of malaria and other mosquito-borne diseases, and may also represent a novel disease prevention approach that is based on an understanding of olfactory receptor genes.

AN Fox, RJ Pitts, HM Robertson, JR Carlson, LJ Zwiebel: Candidate odorant receptors from the malaria vector mosquito *Anopheles gambia* and evidence of down-regulation in response to blood feeding. PNAS 98(25): 14693-14697, December 2001.

New Insights Into Administering Caries Vaccines

Background: When NIH's National Institute of Dental and Craniofacial Research was established, most dental researchers believed a caries vaccine was a biological impossibility. Many noted that because caries-causing bacteria lived in the mouth, then considered outside the body and beyond the reach of the immune system, a vaccine would fail to trigger a protective immune response. Three fundamental discoveries have subsequently established the scientific rationale for a caries vaccine: 1) caries-associated bacteria are transmissible and infectious, 2) the existence of the mucosal immune system, which functions in the mouth, and 3) initial vaccine studies as demonstrated by the generation of a protective immune response against caries-causing bacteria. As specific bacteria in the oral biofilm have been implicated in causing caries, researchers have sought to develop safe vaccines that are easily administered, elicit a sustained immune response, and which target a necessary step in the tooth-decay process. Though a caries vaccine has yet to be developed that meets all of these criteria, the field continues to make steady progress.

Advance: The main target of most caries vaccines is *Streptococcus mutans*, an oral bacterium that a large body of evidence implicates in causing tooth decay. To remain attached to teeth, *S. mutans* must metabolize sucrose to produce a sticky protein polymer that adheres to salivary proteins present on enamel. *S. mutans* performs this reaction using an enzyme called glucosyltransferase, or GTF. Previous work in animals has shown that several synthetic vaccines based on key subunits of GTF can induce a protective immune response in the mouth against the enzyme. Following up on this work, NIH grantees recently evaluated in animals how best to administer a synthetic GTF-based vaccine to induce a protective immune response. The group found that nasal vaccines that were co-administered with other molecules that stimulate the mucosal tissue system, in this case, detoxified cholera holtoxin and *Escherichia coli* heat-labile enterotoxin, were most effective.

Other NIH grantees recently completed a human study that evaluated the relative effectiveness of *S. mutans*-based vaccines administered via the tonsil or the nose. Based on data from 21 adults, 12 of whom were evaluated 18 months post immunization, the scientists found nasal administration to be more effective than via the tonsils. The scientists noted that these results may not be applicable to children, whose tonsils are more functional than adults, and called for a a similar study to be performed for younger populations to identify the proper route, dosage, schedule, and antigen form for a caries vaccine.

Implications: Identifying targets for caries vaccines is just one step in the process. Knowing how to most effectively administer these vaccines to induce immune responses is another. These two studies provide important new data that will enable scientists to develop more effective ways to administer vaccines for future human clinical trials.

Smith DJ, King WF, Barnes LA, Trantolo D, Wise DL, Taubman MA: Facilitated intranasal induction of mucosaland systemic immunity to mutans streptococcal glucosyltransferase peptide vaccines. Infect Immunity 69(8)4767-4773, 2001.

Childers NK, Tong G, Li F, Dasanayake AP, Kirk K, Michalek SM: Humansimmunized with Streptococcus mutans antigens by mucosal routes. J Dent Res 81(1): 48-52, 2002.

Unique Compound Discovered to Halt Tooth Decay

Background: Fluoride has been extremely beneficial in reducing the nation's once rampant rate of dental caries. However, studies indicate that fluoride might interfere with, not directly prevent, the early stages of tooth decay. Given this shortcoming, alternative science-based strategies are needed that complement existing fluoride products and might help to reduce further the rate of dental caries in America. One potential strategy is to target a group of enzymes called glucosyltransferases. GTFs are produced by the planktonic, or free-floating form of *Streptococus mutans*, an oral bacterium that is strongly implicated in causing tooth decay. GTFs produce sticky glucons from dietary sucrose that allows free-floating S. mutans to further anchor itself to enamel and may assist in the bacterial colonization of other species to the tooth surface.

Advance: A team of NIH grantees has discovered that a compound called apigenin is more effective than any agent ever identified in blocking GTFs. Apigenin is one of myriad compounds found naturally in bee glue, or propolis, which honeybees use to repair and protect their hives. The discovery is particularly unique because apigenin can inhibit GTFs both in solution and absorbed to a surface, such as sucrose. Some previously tested compounds have inhibited GTFs in solution only.

Implications: With further safety testing, apigenin could be included as an ingredient in toothpastes, mouthwash rinses, and sprays. It is also possible that products containing apigenin also might be used in isolation. After a meal, people could to chew gum that includes this compound to prevent the maturation of dental plaque.

Koo H, Rosalen PL, Cury JA, Park YK, and Bowen WH: Effects of compounds found in propolis on *Streptococcus mutans* growth and glucosyltransferase activity. Antimicrobial Agents and Chemptherapy 46: 1302-1309, 2002.

Cardiovascular Disease and Kidney Disease: Teasing Out the Link

Are two diseases related or just coincident? Sometimes the answer comes through careful analyses of large sets of numbers – numbers of patients and their associated risk factors. In the case of kidney disease and cardiovascular disease, such epidemiological studies have pointed out a connection between ESRD and risk of CVD. Now researchers are faced with teasing out answers to the question: why?

The United States Renal Data System (USRDS) was established in 1987. The USRDS is "a national data system that collects, analyzes, and distributes information about end-stage renal disease (ESRD) in the United States" and is directly supported by the NIH in conjunction with the federal Centers for Medicare and Medicaid Services (CMS). Through Medicare, CMS provides coverage to most persons who have end stage renal disease (ESRD), a state of irreversible kidney failure in which a person requires either dialysis or a kidney transplant in order to stay alive. The USRDS has collected comprehensive data on over 92 percent of Americans with ESRD, classifying them by numerous criteria, including co-existing conditions at the time of entry into the system, time they have been on dialysis, conditions that develop during dialysis, period incidence, period prevalence, survival on dialysis, and survival post-kidney-transplant. Every year, the USRDS releases these figures as an "Annual Data Report," or ADR; these data can then be analyzed by researchers to discover emerging trends in both causes of ESRD and causes of death in ESRD patients.

A pronounced connection between ESRD and death due to cardiovascular disease (CVD) in a small number of patients on hemodialysis was noted nearly three decades ago. However, it has been the careful analysis of patient data available in the USRDS database that has enabled researchers to recognize the enormity of the connection between patients requiring dialysis and their subsequent deaths from CVD. According to the latest ADR (2001), CVD (defined primarily as coronary artery disease, left ventricular hypertrophy, atherosclerotic heart disease, and congestive heart failure) is the leading cause of death in ESRD patients. Studies using recent USRDS data have revealed that death rates from CVD-related outcomes in dialysis patients are 20 to 40 times higher than in the general population, and an extensive retrospective study showed that 72 percent of dialysis patients who suffer a heart attack are dead within two years of follow-up.

The figures for mortality due to CVD in ESRD are striking – and ominous. Groups at highest risk for developing ESRD includes the estimated 17 million Americans with diabetes, the elderly, and ethnic minorities – all large and growing segments of the population – as well as persons with hypertension, genetic renal disease, or a family history of renal disease. But what is the underlying connection between CVD and kidney disease? The population at risk for developing CVD – independent of ESRD – is very similar to the population at risk for ESRD. In fact, some of the risk factors for CVD are indistinguishable from those for ESRD. Furthermore,

researchers recently reported a higher prevalence of many traditional CVD risk factors in ESRD patients than in the general population.

Studying the USRDS numbers, epidemiologists realized that rates of pre-existing CVD in persons initiating dialysis ("incident" patients) are very high – approximately 40 percent. This led researchers to suspect that CVD is developing during pre-ESRD states. Before ESRD, there is a prolonged state of progressive loss of renal function, referred to as chronic kidney disease (CKD). The degree of CKD is established by measuring how quickly the kidneys are able to clear toxins from the blood, known as the glomerular filtration rate, or GFR. When GFR decreases, bloodstream levels of a number of waste products, including creatinine, increase. Small studies have recently indicated that, just as in ESRD, there are higher rates of death due to CVD in people with CKD. One non-government-supported study found an association between increased creatinine levels and a three-fold increase in mortality from CVD, as opposed to death from renal failure. However, large, prospective cohort studies will be necessary to determine whether CKD generates "novel" risk factors for CVD. It remains possible that CVD and CKD develop independently in an individual with a common set of risk factors, and that CKD is simply a good surrogate marker for the development of underlying CVD. A recently launched prospective study, the "Chronic Renal Insufficiency Cohort (CRIC)," will assess risk factors for both the progressive decline in kidney function and the development of CVD in a large study population with CKD. Through careful data analysis, the researchers aim to determine whether CKD causes CVD or is simply associated with it.

Although defining the link between CKD and risk factors for developing CVD awaits the outcome of large prospective studies, researchers can still test ideas as to how factors traditionally associated with decreasing renal function – uremia related factors – might in fact also lead to CVD. Such factors include electrolyte imbalance, high triglyceride levels, anemia, and elevated toxin levels in the blood. Basic research studies have contributed significantly to a number of hypotheses about how observed uremia-related factors might increase the risk of developing CVD, including the following:

Uric Acid: Uric acid is a waste product of nitrogen metabolism. It is normally present at fairly high levels in the bloodstream, where it is thought to act as an antioxidant. Impaired renal function can lead to increased bloodstream levels of uric acid, causing gout. Elevated bloodstream levels of uric acid also appear to be associated with a greater risk of heart disease, although the epidemiological data are still under debate. A recent study in rats has suggested a possible mechanism for uric acid's proposed role in CVD, showing that artificially induced elevation of uric acid increases blood pressure and causes renal injury by affecting the renin-angiotensin and nitric oxide systems. The candidate human gene encoding the uric acid transporter responsible for uric acid recovery from the kidney tubules, *URAT1*, was recently identified and characterized by a research team in Japan; now, its activity in CKD and ESRD can be tested.

Salt-sensitive Hypertension: There is evidence in animal models that subtle renal injury, induced by local inflammation and vasoconstriction, may interfere with normal salt excretion from the kidneys. Sodium dysregulation in particular may in turn contribute to both high blood pressure and further damage to the kidney, initiating a vicious cycle, and result in permanent salt-sensitive hypertension that promotes CVD.

Homocysteine: Homocysteine is a modified form of the essential amino acid methionine. Normal bloodstream levels of homocysteine (hcy) are maintained primarily by the activities of folic acid and vitamin B_{12}, which reverse the modification of methionine, and vitamin B_6, which regulates a further modification of hcy. Deficiency in these vitamins can lead to hyperhomocysteinemia (Hhcy) – as can decreased GFR. Mild to moderate Hhcy appears to contribute to CVD outcomes in both the general population and persons with ESRD. Although a mechanism has yet to be determined, *in vitro* evidence has suggested as possibilities endothelial cell injury, promoting proliferation of endothelial cells and platelets, and promoting blood clot formation. Although successful in the general population, B-vitamin supplementation is not successful in lowering hcy in ESRD patients; however, it does normalize hcy in both renal transplant patients and mild CKD patients, whose GFRs and degree of Hhcy are similar. A study ("FAVORIT") has now been launched to test whether high-dose supplementation with folic acid, vitamin B_{12}, and vitamin B_6 will improve CVD outcomes in a population of both CKD patients and stable renal transplant patients.

The formulation of testable hypotheses regarding mechanisms by which CKD might induce CVD is crucial for two reasons. First, it will permit researchers to shore up epidemiological data with mechanistic data to explain any observed link between CKD and CVD. Second, testable hypotheses are key to moving towards possible prevention and intervention measures for CVD induced by CKD. Through these efforts, future analysis of figures from the USRDS will hopefully become the more optimistic task of documenting a steady reduction in CVD-related mortality in patients with ESRD.

Brief Interventions for "Risky" Drinking

Nearly two-thirds of all Americans drink beer, wine, or liquor at least occasionally. Most of them, of course, are not alcoholics. However, more than 70 percent of drinkers aged 21 or older exceed the Department of Health and Human Services and the Department of Agriculture guidelines for low-risk drinking: up to two drinks per day for men and one drink per day for women and older people.

High-risk drinking by non-alcoholics is a significant cause of motor vehicle crashes, injuries, illnesses, and other alcohol-related problems. Because these so-called "risky drinkers usually do not visit alcohol treatment specialists, they present a challenge for clinicians and researchers. Many, however, are likely to have regular contact with a family doctor or other healthcare provider. NIH-supported researchers and other scientists believe primary caregivers can help encourage moderate drinking habits. Recent years have seen the development of strategies to enable primary caregivers to identify and treat risky drinkers.

Brief intervention has emerged as perhaps the most promising way to address risky drinking among non-alcoholics. It is a time-limited strategy focused on changing behaviors and typically consists of four or fewer sessions lasting from a few minutes to an hour. The basic elements of a brief intervention include an assessment of how much and how often a patient drinks, as well as questions about any alcohol-related problems the patient has experienced. If the patient's responses indicate high-risk alcohol use, the healthcare provider advises the patient to quit drinking or establishes a goal for reducing the patient's drinking, and suggests specific ways to help the patient attain the goal. The healthcare provider monitors the patient's progress through follow-up office visits and supportive telephone consultations.

Researchers in the United Kingdom first demonstrated the effectiveness of brief intervention in primary care settings in the late 1980s and early 1990s. One study, for example, found that after one year, alcohol consumption had declined among high-risk drinkers who received two brief interventions from their doctors followed by two supportive phone calls. The patients also had reduced blood pressure and healthier liver enzyme levels.

In 1997, NIH-supported scientists in the U.S. reported the results of Project TrEAT (Trial for Early Alcohol Treatment), the first large-scale study of the effectiveness of brief intervention in this country. The study found that two physician counseling visits of 10 to 15 minutes each followed by two 5-minute follow-up phone calls led to significant reductions in drinking among high-risk drinkers. Sustained reductions in drinking have been seen in Project TrEAT participants after four years of follow-up. Project Health, a subsequent NIH-funded study published in 1999, also demonstrated significant reduction in alcohol use by high-risk drinkers following 5- to 10-minute brief interventions.

NIH-supported researchers recently have extended the brief intervention concept to the emergency room setting. In a 1999 study, patients admitted to a trauma center for alcohol-related injuries took part in a single motivational interview with a psychologist. One year later, the patients' alcohol use had decreased significantly, particularly among those who initially had mild to moderate drinking problems. Another 1999 study evaluated the use of a 30-minute motivational interview in the ER among adolescents who had been involved in alcohol-related events. Six months later, the adolescents who received the motivational interview had lower rates of drinking and driving and fewer traffic violations and alcohol-related injuries, compared with patients who received standard care.

Within the past 5 years, scientists supported by NIH have shown that brief intervention is effective for reducing problem drinking in specific groups of problem drinkers. Alcohol-related health problems are common among elderly persons. In fact, an estimated 15 percent of men and 12 percent of women over the age of 60 regularly drink in excess of the recommended limits. In Project GOAL (Guiding Older Adult Lifestyles), NIH-supported researchers found that alcohol use was significantly reduced among older adult problem drinkers who received two brief counseling sessions from their doctors.

Researchers also have found that heavy-drinking college students who received a one-hour counseling session and a discussion of drinking risks and norms decreased their alcohol use and binge drinking over two years. In addition, individual motivational interviews with high-risk drinking freshman reduced their alcohol use and alcohol-related problems.

Gene Therapy Approaches to Sight-Threatening Uveitis: Reprogramming the Immune System for Self-Tolerance

Intraocular inflammatory disease known as uveitis is a commonly seen ocular disorder that mainly affects children and young adults. It has been estimated to cause about 10 percent of the severe visual handicap in the United States and if untreated can rapidly lead to blindness. Some ocular inflammations may be due to an infectious agent. However, a large number of intraocular inflammatory conditions appear to be due to an altered immune response of the body to itself, known as autoimmunity, where the body attacks its own tissues much as it would a transplanted organ. In uveitis the target proteins appear to reside in the retina of the eye. Animal models for autoimmune uveitis have helped enormously to understand this abnormal immune response and to evaluate candidate therapies.

The present therapies for autoimmune uveitic disorders are drugs that suppress the immune response (immunosuppressants). Although these drugs can be very effective in treating uveitis, they have significant side effects in terms of toxicity and also supress beneficial immune responses to viruses and bacteria. The goal of scientists is therefore to better understand the underlying mechanisms that lead to autoimmunity and ocular inflammation, so as to more specifically turn off only the harmful response, and try to do so with minimal or no side effects.

We have shown that a central mechanism in uveitis appears to involve a population of lymphocytes known as T-cells that recognize and attack foreign proteins (antigens) but normally leave alone the antigens composing self tissues. Because the eye is an immunologically privileged organ that is immunologically closed off from the rest of the body early in development, it is not recognized as self tissue. Scientists hypothesized, therefore, that if the ocular proteins (antigens) targeted in uveitis were removed from their immunologically privileged status and expressed outside of the eye in healthy tissues accessible to the immune system, it might be possible to re-educate the autoreactive T-cells to tolerate these antigens.

Using the antigen IRBP (interphotoreceptor retinoid binding protein) that is the target protein in uveitis in mice, these scientists created transgenic mice that were genetically engineered to express IRBP in many tissues of the body, including spleen, gut, kidney and bone marrow. These transgenic mice were extremely resistant to developing uveitis compared to normal mice, and their immune responsiveness to IRBP was reduced as judged by several immunological assays. This constituted proof of concept that expression of a retinal antigen outside the eye can lead to specific immune tolerance without affecting other immunological responses. By transfusing leukocytes from IRBP transgenic mice to normal mice that were susceptible to developing uveitis, the normal individuals also became resistant to the disease. This suggested that gene transfer into normal individuals might constitute a clinically attainable approach to reeducating the immune system for tolerance.

The scientists then explored two methods of gene transfer to achieve extraocular expression of IRBP in normal animals: DNA vaccination and retroviral gene transfer. In the vaccination approach, DNA encoding the IRBP protein was injected intramuscularly or intravenously into mice. Vaccination by either route partly to completely protected mice from developing uveitis and reduced their immunological responsiveness to IRBP. Additionally, DNA vaccination was extremely effective in preventing disease (when vaccination preceded immunization) and was partly effective in reversing disease (when vaccination followed immunization).

In the retroviral gene transfer approach, a fragment of the IRBP gene fused to the gene encoding mouse immunoglobulin was engineered into a retroviral vector that inserted the gene into peripheral B cells (antibody producing cells). Mice that received the modified B cells were protected from uveitis induced by a subsequent immunization with IRBP. Further immunological studies suggested that the harmful T cells were either deleted or inactivated. Importantly, the retrovirally modified B cells were very effective in a reversal protocol when given to mice that had been challenged for disease before receiving the treatment.

Because patients with uveitis are by definition in an immunized state, it is desirable for an effective therapy not only to prevent but also to reverse the disease process. Both gene transfer approaches demonstrated efficacy not only for prevention but also for reversal of the disease process. Currently, the approach of tolerance induction by retroviral transfer of a retinal gene into a patient's own B cells is being adapted for a clinical trial. It is hoped that this innovative and promising approach to the translation of research on ocular immunology will result in a highly effective therapy to alleviate sight-threatening uveitic disease.